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Section of Comparative Medicine

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DISCUSSION ON CHRONIC NEPHRITIS

Dr. Dorothy S. Russell: At the present time there is a general tendency to divide Bright's disease into three groups. (1) Degenerative, which is synonymous with lipoid nephrosis or *nephritis mitis*. (2) Hæmorrhagic, glomerulo-nephritis or *nephritis acris*. This is the form most commonly seen. It is divisible into diffuse and focal varieties. The diffuse can easily be recognized, both clinically and histologically, in three phases: early, intermediate, and late. The focal variety, *nephritis acris repens* or chronic interstitial nephritis, is seldom recognized except in its terminal stages, when secondary cardiovascular hypertrophy is generally a conspicuous feature. (3) Arteriosclerotic (or *ischæmic*) nephritis. This may be present with or without cardiovascular hypertrophy. According to some authorities, there are two varieties that may arise in association with such hypertrophy: benign sclerosis, in which renal insufficiency does not develop, and "malignant sclerosis" in which renal insufficiency and albuminuric retinitis supervene through the operation of some little-understood process. In my experience, cases that are diagnosed clinically as malignant sclerosis are histologically examples of nephritis repens. Reasons will be given later why the existence of malignant sclerosis as a separate histological type seems questionable.

A few of the principal histological features of the chronic forms in groups (2) and (3) will be considered, taking (3) first for the sake of clearness. The histology has been described in detail in a previous publication [1].

In the so-called benign hypertension, or primary ischæmic nephritis, the essential lesion is in the smallest arterioles, namely, the vasa afferentia and arteriolæ rectæ. These vessels participate in the general vascular hypertrophy that accompanies a persistent high blood-pressure. But hypertrophy in these vessels is quickly followed by degeneration. In this the intima is first affected; it becomes swollen, hyaline and acellular. The reduplicated elastic stripe and then the elastic lamella are broken into fragments and later disappear, and the degeneration then spreads outwards to involve the media also. In sections stained for fat a conspicuous

deposit of fatty substances is found in the hyaline area, so that the change is conveniently called a "fatty-hyaline" degeneration. The lumen is narrowed to a thin crescent or a pin-point. There is no endothelial proliferation or other evidence of inflammation.

The effect of this progressive depletion of the blood supply is first shown by the tubules, which atrophy. The glomerulus later begins to shrink; there is a progressive collagenous thickening of Bowman's capsule, the original basement membrane of which is thrown into folds. Still later the tuft loses its nuclei and becomes hyaline. The glomerulus may persist in this state of atrophy, or may be broken up and invaded by small lymphocytes and capillaries. The interstitial tissue about the glomerulus and atrophied tubules is increased in density through thickening of the collagen fibrils; it is often infiltrated with groups of small lymphocytes.

The conclusion that this particular series of changes is truly the result of ischæmia is not based only upon the observed association of the changes described with degeneration of the afferent arteriole. It is based also upon observations of the histological effects produced by degeneration in the larger renal arteries. Thus, if the main renal artery is partly blocked by atheroma, the whole of the kidney is shrunken and fibrotic and all the nephrons are affected in the manner that has been described, making due allowance for the fact that the capsular arterioles provide a circulation in some areas and thereby cause a certain amount of patchiness in the ischæmic effects. Similarly, partial occlusion of an interlobar artery causes a large saucer-like depression in the surface of the kidney, corresponding with a broad wedge of ischæmic atrophy and fibrosis in the underlying area supplied by the artery. Degeneration in the arcuate and interlobular arteries produces smaller "mouse-eaten" areas of atrophy and fibrosis beneath the renal capsule. Degeneration of a large number of vasa afferentia produces an atrophy and fibrosis that is reticular in its distribution, and leads to the well-known granularity of the cortex and distortion of its pattern.

If these changes are accepted as ischæmic, it is then possible to analyse the histological appearances in chronic diffuse nephritis acris and in nephritis repens, where cardiovascular hypertrophy and ischæmic nephritis enter in as secondary complications. In distinguishing true Bright's disease from the effects of ischæmia, the glomerular changes are of the greatest help. As distinct from the ischæmic change, the glomerulus reacts in at least three ways that can be identified with the microscope. These, arranged in order of decreasing intensity of reaction, are: (1) proliferation of the capsular epithelium, or *proliferative capsulitis*; (2) proliferation of the endothelium of the tuft, or *proliferative glomerulitis*; this may go on to a late stage in which hyalinization of the tuft occurs through a gradual loss of the cells; these disappear first from the centres of the lobules; (3) *focal necrosis* of the tuft, with *adhesions* of the tuft to Bowman's capsule. This third reaction is the commonest glomerular lesion in nephritis repens. It commonly occurs at points remote from the hilum. The necrotic area is rich in lipoids and is not fibrinoid; it has no relation to the focal embolic lesion associated with infective endocarditis. It also is a progressive lesion which gradually leads to complete hyalinization of the tuft and its absorption into the stroma of the kidney.

All transitions can be found between chronic diffuse nephritis acris and nephritis repens. The essential feature of the latter is the patchy distribution of inflammation in the cortex, so that islands of variable size and shape are involved later in fibrosis or escape it. If a large number of such kidneys is examined it will be found that they can be arranged in a series leading from the diffuse type, with relatively intense inflammation, to types in which the distribution of the inflammation is most focal and the reaction least severe. It is in examples at the latter end of the series that cardiovascular hypertrophy is usually maximal, and secondary ischæmic nephritis is

conspicuous to a corresponding extent. In the clinical course of such examples, evidence of high blood-pressure may precede any evidence of disturbance of renal function. From comparative histological studies, however, of chronic diffuse nephritis acris and nephritis repens, it was concluded [1] that progressive focal nephritis acris initiated the cardiovascular changes. Actual histological proof of this was not obtained until recently, and is given in a separate communication [3]. The cases in which clinical evidence of disturbance of renal function is preceded by cardiovascular hypertrophy are nevertheless regarded by many as examples of "malignant sclerosis." The chief histological criterion of this malignant sclerosis is generally held to be the presence, in the walls of the small arterioles, of an acute fibrinoid necrosis. This superficially resembles the fatty-hyaline degeneration that has already been described, but differs in that the intima is occupied by a fibrinoid coagulum in which red corpuscles or their ghosts can frequently be seen. The elastic lamella is often destroyed and the media may share in the fibrinoid change. There is sometimes, in addition, an inflammatory infiltration of the adventitia with neutrophil leucocytes, or with cells of resembling histiocytes. This necrotic change is not, however, confined to kidneys of the repens type but, as shown by Fishberg [2] and others, is also seen in examples of subacute nephritis—that is, nephritis acris in the intermediate stage. In these, cardiovascular hypertrophy is absent, or, if present, is only slight. Four examples of fibrinoid necrosis of arterioles in the intermediate stage of nephritis acris are here illustrated:—

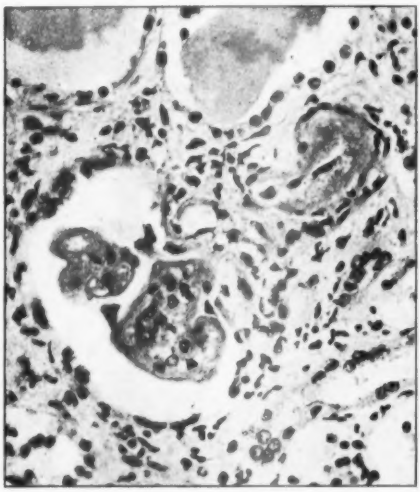

FIG. 1

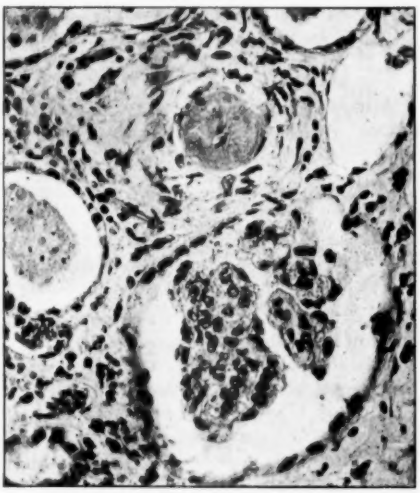

FIG. 2

FIG. 1.—Afferent arteriole in a woman, aged 42, with a five months' history of nephritis with œdema; blood-pressure 150/95; heart weight, 8 oz.

FIG. 2.—Afferent arteriole in a woman, aged 25, with a two or three months' history suggestive of heart failure; blood-pressure 140/90 to 185/120; slight hypertrophy of heart (11¼ oz).

It seems reasonable, therefore, to suppose that this acute arteriolar necrosis is due to the action of a toxin that is intimately associated with nephritis acris and is not essentially associated with cardiovascular hypertrophy. There appears to be no

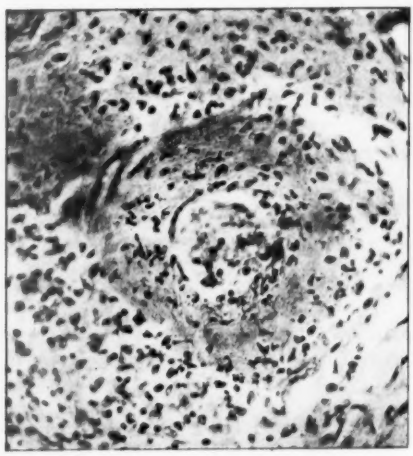

FIG. 3

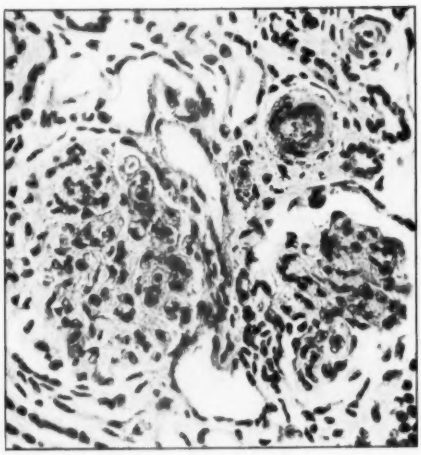

FIG. 4

FIG. 3.—Interlobular artery in a woman, aged 34, with a two months' history of nephritis following quinsy; blood-pressure 133/83; possibly slight hypertrophy of heart (11 oz); conspicuous infiltration of the adventitia with neutrophil leucocytes.

FIG. 4.—Afferent arteriole in a girl, aged 4, with a four weeks' (possibly longer) history of nephritis; blood-pressure 165/120; slight hypertrophy of heart (4 oz.).

adequate reason for the separation of a distinct type of Bright's disease on the basis of the presence of this arteriolar lesion.

REFERENCES

1 RUSSELL, DOROTHY S., A classification of Bright's disease, 1929, *Med. Res. Counc. Sp. Rep. Series*, 142.
2 FISHBERG, A. M., *Arch. Int. Med.*, 1927, xl, 80.
3 RUSSELL, DOROTHY S., *Journ. Path. and Bact.*, 1934, xxxviii, 179.

Professor J. Duguid: I wish to describe a type of chronic nephritis which can be produced in rats by overdoses of vitamin D combined with a diet rich in acid sodium phosphate. Hypervitaminosis D causes calcification of the kidneys, and this is sometimes accompanied by a slight tubular nephritis. In the course of an investigation being pursued in the Department of Pathology of the Welsh National School of Medicine on the problem of renal calcification, the effect of altering the reaction of the urine was tried. During the course of vitamin D treatment, rats were given diets rich in phosphates: acid sodium phosphate to produce an acid reaction, and di-sodium or tri-sodium phosphate to maintain an alkaline urine. A paper describing the results has been published (Gough, Duguid and Davies, 1933). On the whole, the administration of phosphates increased the renal calcification, but the acid and alkaline phosphates respectively produced somewhat different effects on the kidney. Whereas the alkaline phosphates caused a very marked increase of calcification, the acid phosphate produced a very severe tubular nephritis. This nephritis was of the type often seen in a mild degree in hypervitaminosis D, but it now appeared with astonishing severity. It was also found that acid sodium phosphate alone, and, to a slight degree, other phosphates, could produce lesions of this kind, if administered over very long periods or in very large doses, as had already been shown by Hirsch (1923), and by MacKay and Oliver (1930). The condition, therefore, was probably a

phosphate nephritis, but the lesions produced by phosphate alone were very mild in comparison with those produced by acid sodium phosphate combined with overdoses of vitamin D.

This experimental nephritis in rats is of considerable pathological interest. It can be produced with ease and certainty by a short course of treatment which, in most cases, causes comparatively little interference with health in the early stages. Once started, it goes on to the development of a chronic progressive nephritis of extreme severity, such as has not previously been obtained, I believe, in animals experimentally (fig. 1). The most important feature, however, is that, whilst it is primarily a tubular nephritis, it leads in its later stages to interstitial fibrosis, glomerular atrophy, and arterial thickening, all of which are looked upon as important essentials, and some of them as causal factors, in the chronic nephritis of man. The experiments, in fact, furnish evidence that glomerular and arterial lesions can be results, rather than causes, of chronic renal atrophy.

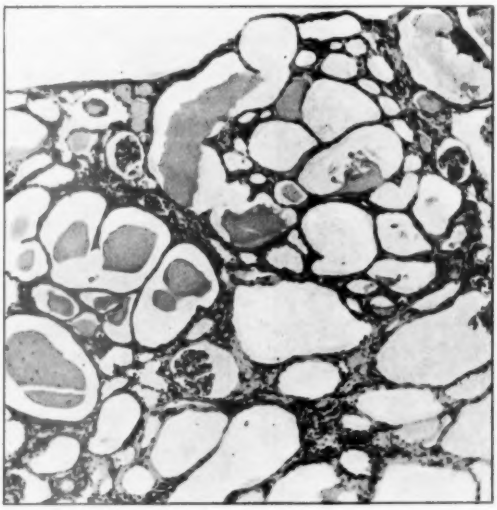

FIG. 1.—Chronic nephritis in rat, 101 days after the end of treatment (× 70).

I have set out a demonstration of an experiment, which has been on the whole the most successful one in a series in which there have been tried a variety of combinations and dosages of vitamin D with acid sodium phosphate. A group of 11 rats were given, over a period of 25 days, a standard diet of bread and potatoes (70 : 30 parts respectively), to which was added acid sodium phosphate (5 parts). During the last twelve days the rats also received daily, *per os*, 40,000 units of vitamin D (calciferol) in olive oil. On the twenty-fifth day one was killed and, as its kidneys were found to be severely affected, the rest were put on a normal mixed diet and allowed to recover. They survived for varying periods up to 160 days. Incidentally, in other experiments animals have survived for periods up to 650 days after this or similar treatment. They showed intense albuminuria, and many developed polyuria. Post mortem, as will be seen from the demonstration, all were found to have severe nephritis, with widespread destruction of the parenchyma.

The nephritis is essentially a tubular one, with necrosis and atrophy of large groups of tubules and dilatation of others with flattening of their epithelium. A certain amount of fatty change is usually present. The atrophied tubules collapse and disappear, and the supporting reticular framework of the kidney becomes shrunken and condensed, until finally it becomes fused into masses of fibrous tissue. It has been possible to follow this process of interstitial fibrosis through different stages, and, contrary to the general teaching in relation to chronic nephritis in man, it has been found to be practically independent of fibroblastic proliferation. The process apparently consists of a condensation and fusion of the reticulum fibres and later there is metamorphosis of these into collagen fibres. In the earlier stages of the nephritis the glomeruli are entirely unaffected, but later retrogressive changes begin to appear in them, consisting of distension of Bowman's capsule with exudate (fig. 2), adhesions and thickening of the capsule (fig. 3), hyaline degeneration of the

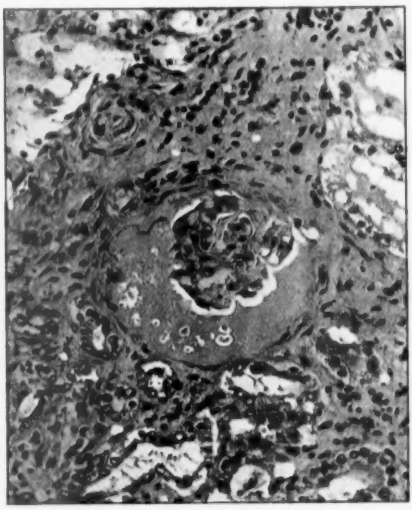

FIG. 2

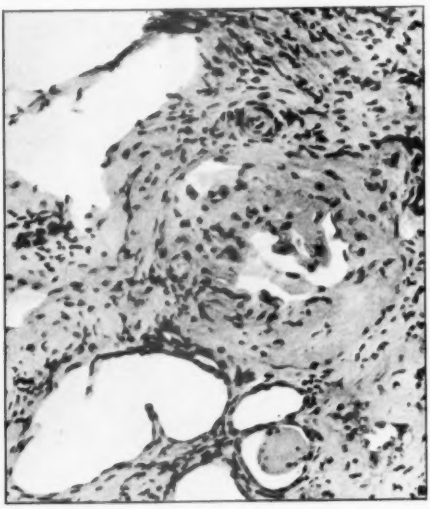

FIG. 3

FIG. 2.—Exudate in glomerular capsule (× 170).
FIG. 3.—Hyaline degeneration and adhesion of glomerular tuft (× 200).

tufts (fig. 4) and, finally, complete atrophy. In long-standing cases vascular changes begin to appear. At first, there is prominence of the vessels in the cortex, suggesting hypertrophy of their walls; later there is definite proliferation, both in the arterioles, where an appearance simulating arterio-capillary fibrosis is produced (fig. 5), and in the larger arteries, where there is proliferation of the intima (fig. 6) and splitting of the internal elastic lamina.

When an attempt is made to correlate these observations with the pathology of chronic nephritis in man, the importance of the findings in the arteries becomes evident. Arterial lesions such as these are characteristic of the human disease, and are commonly accepted as the cause of certain manifestations of it. In this experimental nephritis, however, the lesions are clearly a result of the parenchymatous change, since they occur only in cases where the latter is severe and of long standing. I believe that they represent a process comparable with that seen in the involuting

uterus, and that they are caused by the diminution in the capacity of the capillary field. In the kidneys of the experimental rats the parenchyma becomes extensively

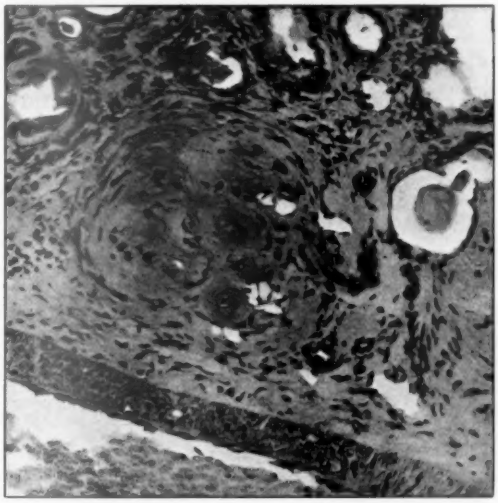

FIG. 4.—General hyaline transformation of glomerus and afferent arteriole (× 200).

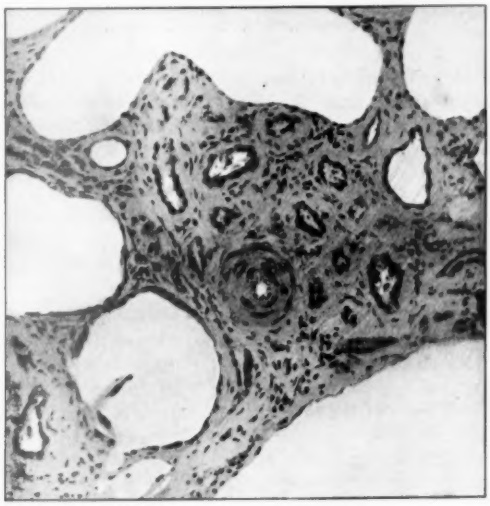

FIG. 5.—Arteriolar thickening (× 145).

shrunken and fibrosed, whilst large numbers of glomeruli are destroyed, so that there must obviously be restriction of the circulation and, as a result, diminution of the vascular lumena.

I have long held the opinion that the arterial lesions in some forms of so-called arteriosclerotic nephritis in man are of similar nature: in other words that they are a natural result of the shrinkage of the kidney and not a cause of it. Morphologically,

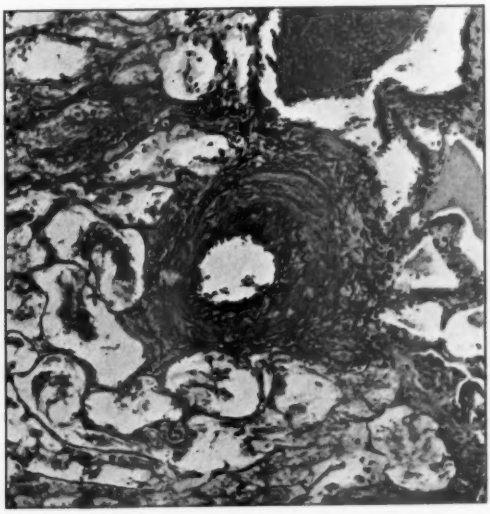

FIG. 6.—Arterial lesion in a rat which died 325 days after treatment (Weigert's elastic tissue stain and v. Gieson, × 160).

this experimental nephritis in rats has many points of similarity to the primary atrophic nephritis of man, and the fact that arterial disease can occur as a consequence of chronic parenchymatous degeneration in the rat seems sufficient to indicate that the same process can happen in man.

REFERENCES

GOUGH, J., DUGUID, J. B., and DAVIES, D. R., *Brit. Journ. Exper. Path.*, 1933, xiv, 137.
HIRSCH, E. F., *Arch. Int. Med.*, 1923, xxxi, 862.
MACKAY, E., and OLIVER, J., *Proc. Roy. Soc. Exper. Biol. and Med.*, 1930, xxviii, 324.

Dr. Tom Hare: Nine years ago I began collecting material for a systematic study of the pathology of nephritis in the dog. I propose to summarize briefly my records of nearly 150 cases of nephritis and nephrosis in dogs, all of which were submitted to a comprehensive post-mortem and histological investigation. The post-mortem examination was made within 24 hours of death.

Before passing to chronic idiopathic nephritis of the dog I will name, and so eliminate from further consideration, the types of inflammatory and degenerative lesions of the kidney which were represented in my material.

A.—Acute nephrosis, i.e. an acute tubular and glomerular degeneration unaccompanied by inflammatory changes and due to, or directly associated with, the following fatal intoxications:

(1) Poisoning by phosphorus, cyanides, and halogen anæsthetics;

(2) Intussusception of the jejunum, leading to fatal acute intestinal obstruction, pregnancy toxæmia of the bitch, and diabetes mellitus;

(3) Deep jaundice, due to carcinoma of the head of pancreas (two cases) and to leptospiral infection (one case);

(4) Bronchopneumonia associated with rickets and secondary to distemper; acute adenitis of the ileocæcal mesenteric gland (due to streptococci or *Bact. coli*);

(5) The so-called "acute hæmorrhagic gastro-enteritis," so commonly met with in racing greyhounds, which I believe to be an allergic state occasioned most probably by food idiosyncrasy.

B.—Nephritis due to certain specific causes, e.g.:

(1) Ascending nephritis (pyelonephritis) associated with acute septic prostatitis, fibrocystic enlargement of the prostate, septic metritis, calculus, neoplasia with urinary obstruction, following catheterization and other surgical interferences with the lower urinary tract;

(2) Tuberculosis, in its descending or miliary form or in its ascending form secondary to tuberculous orchitis or prostatitis;

(3) Leukæmia (assuming it to be due to a filtrable virus), which is invariably fatal.

C.—Arteriosclerotic kidney: one case only, in a male, aged 7 years; eleven months history of stiff back and chronic rheumatism; destroyed; autopsy revealed hypertrophied left ventricle, extensive atheroma of the aorta, generalized medial degeneration of the smaller arteries, chronic infarcts in lung and small intestine, spondylitis deformans and osteo-arthritis of both femorotibial joints.

Chronic idiopathic nephritis.—Of 23 cases I have made an arbitrary histological classification of five as the early, and 18 as the late, stage of chronic nephritis, though from the clinical notes no differences could be determined between them.

TABLE I.

Type	No. of Cases	Age in Years. Range	Mean	Sex. Male	Female	Duration of Uræmia. Range	Mean
Early	5	4 to 8	6	4	1	7 to 9 days	8 days
Late	18	2½ ,, 14	7½	15	3	½ ,, 16 ,,	7 ,,

Clinically, both histological types were characterized by an insidious onset; eleven had been under veterinary observation for more than one month, on account of intermittent attacks of a vague dyspepsia; with the remaining twelve cases, the premonitory symptoms were not recorded or not observed. The 23 cases were brought for professional attention because of the onset of uræmia, which was frequently precipitous and alarming to the owner.

Uræmia, in the dog, is characterized by:—

(1) Apathy, anorexia, abnormal thirst, and drowsiness, followed by (2) vomiting, frequently hæmatemesis, melæna, constipation, occasionally diarrhœa, urinary odour of the breath, petechial hæmorrhages leading to erosions of the mucosa of the tip and borders of the tongue and of the mouth, sometimes bleeding from the gums, fibrillary muscular twitchings, progressive weakness, anæmia, subnormal temperature, prostration; (3) finally semi-coma, ending in death. At autopsy, multiple hæmorrhagic erosions are also found in the mucous membrane of the fundus of the stomach and commonly of the first inch of the duodenum; catarrhal gastritis and duodenitis; hæmorrhagic mucinous contents of the stomach and small intestine; congestion and frequently petechiæ of the mesentery; sometimes hæmorrhages into the retina, pleura and endocardium; central zone necrosis of, and multiple capillary hæmorrhages into, the liver; albuminous degeneration of the myocardium and commonly an early stage of aspiration bronchopneumonia. In addition, there are the changes in the urine and in the kidneys, which may reveal late acute, subacute or chronic nephritis of the ascending or descending types. For the past seven years I have frequently demonstrated that uræmia in the dog has been mistakenly regarded as a specific infection, which under the name of Stuttgart disease, had crept from Germany into English veterinary literature.

Of the 23 cases of chronic nephritis, 10 died naturally and 13 were destroyed at their owner's request, 12 in the late and one in the early stages of uræmia. At autopsy, no constant lesions were found other than those of uræmia and nephritis. Hypertrophy of the left ventricle was present in nine cases, in seven of which it was associated with quiescent chronic mural or mitral endocarditis. Œdema was not observed at autopsy or recorded in the clinical notes, nor were blood-pressure readings recorded. The urine, which was examined either during uræmia or at autopsy on the day of death, revealed a lowered specific gravity (1008 to 1020), polyuria, albumin—from traces to moderate amounts—and, usually, hyaline—and occasionally, granular—casts.

The kidneys of the late type were contracted (usually equally), with an opaque and thickened capsule which was invariably adherent to the prominent interlobular septa and usually adherent over the greater part of the cortex. Usually the cortex was pale, sometimes reddened; in one case one kidney was red and the other pale. The surface of the cortex was usually finely granular, sometimes coarsely roughened and showing minute cysts. Usually, on hemisection the demarcation was blurred; the opaque pearly pale (or congested) cortex was reduced in width, and the medulla was pale (or congested), opaque, very tough and contracted. Cysts, usually very small, sometimes up to pin-head size, were scattered within the cortex and medulla. The larger blood-vessels were more prominent. Microscopically, there was a considerable increase in the reticulum, due to fibrous tissue, which was more dense and usually hyaline along the interlobular septa, around the atrophied glomeruli and tubules, and around the larger arteries within the intermediate zone. The new fibrous tissue was younger and more delicate adjacent to the regenerated and hypertrophied glomeruli and tubules. Usually, small lymphocytes, with occasional neutrophil leucocytes and plasma cells, were collected in the form of wedges along the interlobular septa, the base of the wedges being at the surface of the cortex, but there was no diffuse infiltration. Many glomeruli and tubules had been obliterated. All degrees of shrinkage and deformity were seen in the glomerular tufts, many were adherent and many were wholly or partially hyalinized, with thickened hyalinized capsules and pericapsular fibrosis. There were no epithelial crescents. Groups of glomeruli were hypertrophied. The majority of the tubules were dilated, many were shrunken and atrophied; most of them contained hyaline, and sometimes granular, material, degenerated epithelium and occasional neutrophil leucocytes. The number of regenerated tubules varied in different cases. Lipoid was always present but its quantity was variable. In all cases there was a definite peri-arterial fibrosis and, as a rule, the lumen of the arteries was reduced owing to medial hypertrophy and hyaline thickening of the intima.

By comparison, the kidneys of the early type were only slightly shrunken, and the capsule, though adherent to the interlobular septa, stripped from the slightly granular and blotchy surface. There were no cysts. However, the arbitrary division into early and late types was only made after histological examination. In the early type, the diffuse increase of the reticulum was pronounced, but it was composed of a more cellular and slightly œdematous fibrous tissue. The infiltration of lymphocytes, plasma cells and a larger proportion of neutrophil leucocytes was more abundant and more diffuse. Many glomeruli were hyalinized, but the majority of the tufts were lobulated and adherent to partially hyalinized and shrunken epithelial crescents. Neutrophil leucocytes were found in some of the tufts. There was less atrophy of the tubules, their most prominent change being hypertrophy with widespread necrosis or degeneration and desquamation of their epithelium. The artery walls were not hypertrophied.

The ætiology of chronic idiopathic nephritis.—The incidence of acute descending nephritis in the dog is very much lower than that of chronic nephritis. I have four cases of acute pyæmic nephritis in puppies under one year old which were due to

Bact. coli pyæmia secondary to acute enteritis. I have collected in Table II some data of my eight remaining cases of acute descending nephritis.

TABLE II.

Case No.	Sex	Age	Clinical course	Type of nephritis	Type of infective endocarditis
1	F.	5	5 days	Acute pyæmic	Acute
2	M.	2	8 ,,	,, ,,	,,
3	F.	3½	4 ,,	,, ,,	Subacute
4	M.	3½	4 ,,	Subacute focal	,,
5	M.	1½	14 ,,	,, ,,	,,
6	M.	5	7 ,,	,, ,,	,, (mild)
7	M.	2¾	14 ,,	,, ,, (late)	,, ,,
8	M.	1½	8 ,,	Acute diffuse	,,

Cases 1, 2 and 3 do not call for special comment; they showed the typical symptomatology and pathology of infective endocarditis, and streptococci were isolated from the heart blood of 1 and 2 at autopsy. The remaining five cases, though secondary to infective endocarditis, presented symptoms of acute nephritis with albuminuria and hæmaturia (Cases 4 and 5) with acute uræmia terminating in death in semi-coma. Cases 4, 5, 6 and 7 are arranged in sequence according to the duration of the reaction as observed histologically in the kidneys. In these four cases the metastatic lesions were confined to the kidneys (histologically); in No. 6 occasional diplococci were observed in some of the focal renal lesions, the others appeared histologically to be free of bacteria. Histologically the nephritis of No. 8 was of the acute diffuse type without bacteria being found.

Upon so few cases it would be absurd to generalize. I have cited these cases because I have formed the impression that with my collection of chronic nephritis they reveal an orderly sequence of pathological events. Though it is very unusual for dogs to die with an acute or subacute nephritis, the cases which I have collected in nine years have certainly been due to infection.

Chronic nephritis associated with osteoporosis.—Finally, I wish briefly to summarize my observations on eleven cases of a syndrome, of which I have found no description in the literature. This syndrome consists of the association of chronic nephritis with osteoporosis. The eleven cases comprised dogs of various breeds; ten males and one female; and ranged in age from 6 months to 11 years (mean age = 5½ years). The clinical picture was dominated by osteoporosis of the skull, which colloquially is known as "rubber jaw." The owners had sought veterinary advice because the dogs did not prehend and masticate solid food properly for periods extending from two to twelve weeks (mean period of four weeks). On admission the skull bones were so soft that manual examination, which the patients usually resisted, commonly resulted in fractures of the inferior maxillæ or of the cranial vault. Seven cases showed uræmia; an eighth case revealed three typical attacks of tetany during the fortnight preceding its destruction.

At autopsy the softened bones of the skull were swollen and spongy; their spaces contained a red—and usually firm—marrow. In three cases the marrow hyperplasia was excessive, producing marked swelling of the superior and inferior maxillary bones. Histologically, the osteoporosis of the skull was an osteitis fibrosa. An early stage of the disease was found in the shafts of the ribs of three cases, in two of which the femora were also slightly affected. No evidence of rickets was found. Despite the difficulties of masticating solid food, only two cases showed evidence of emaciation.

All cases revealed swollen submaxillary and cervical lymphatic glands and in four cases the tonsils and axillary lymphatic glands were also enlarged. Histologically, the swelling of these glands was due to an endothelial cell hyperplasia and to large accumulations of calcium and blood pigment within the sinuses. In four

cases metastatic deposits of calcium were also found in the thyroid glands, in the submucosa of the epiglottis, beneath the endocardium of the left ventricle and within the liver and lung. In three cases the parathyroid glands were enlarged by about 50 %, owing to a simple epithelial hyperplasia (not adenoma). The thyroid glands were enlarged by 100% due to hyperthyroidism in two cases and to simple goitre in one case; in a fourth case the thyroid glands were atrophic and very fibrous. Histologically, in all cases, the gonads, pituitary and suprarenal glands revealed no abnormality.

Anæmia was evident in all cases at autopsy, but in only one case was it possible to make a blood-count preceding destruction; this revealed 2,160,000 R.B.C., 16,250 W.B.C., 526,000 platelets, neutrophil leucocytosis (76·3%), poikilocytosis and anisocytosis; no normoblasts or megaloblasts were observed. Broth cultures of the blood remained sterile up to ten days' incubation aerobically at 37° C. Histologically, no parasite was found in the tissues of any case.

The macroscopic and microscopic appearances of the kidneys differed in only one respect from those of chronic (idiopathic) nephritis. The additional change was the presence of calcium phosphate in large amount within the pelvis and tubules and small deposits within Bowman's capsule, glomerular tufts and basement membrane of the tubular epithelium. Iron, as blood pigment, was also present with the calcium.

The urine of all cases was turbid, owing to a heavy content of calcium phosphate; the specific gravity ranged from 1010 to 1025; hyaline and occasional granular casts were present; slight albuminuria was present in ten cases and absent in one case.

I have come to the conclusion that in this syndrome the nephritis develops insidiously and precedes the onset of the localized osteoporosis, but the initial cause remains a mystery.

A terrier, aged one year, and showing well-developed osteoporosis of the skull, swollen submaxillary glands, albuminuria, and slight anæmia was brought for destruction. One of my colleagues persuaded the owner to give the dog to me. He was taken home by one of my senior students and carefully nursed and fed on mixed raw meat and bones, with water and milk to drink. The anæmia and albuminuria disappeared, the skull bones became calcified in their swollen form thus leaving the dog with a pronounced undershot lower jaw. Otherwise he appeared to retain perfect health until last week when he was destroyed because of his vicious temper. An autopsy was made immediately. Both kidneys were congested, tougher than normal, with adhesions to the interlobular septa and pitting of the surface of the cortex. The swellings of the softened skull bones due to hyperplastic marrow had been converted into dense cancellous bone. No other abnormalities were found in the carcass and no albumin was found in the urine. There has not yet been an opportunity of studying the histology but the observations made in this case show that the progress of this syndrome may be arrested.

Conclusions.—From personal observations of *descending* nephritis in the dog it is suggested that:—

(1) The incidence of fatal acute descending nephritis is very low and such cases are probably always of infective origin;

(2) The incidence of chronic nephritis is at least three times greater; it develops insidiously and causes little noticeable ill-health (except when associated with osteoporosis) until the onset of uræmia;

(3) Histologically there is an orderly sequence of changes from the acute and subacute (infective) nephritis to the chronic nephritis, indicating that, sometimes at least, the latter is the result of a descending infection.

(4) Dogs dying of various types of severe intoxication commonly show acute nephrosis, but the possibility of milder non-fatal intoxications eventually producing renal changes indistinguishable from chronic nephritis cannot be excluded;

(5) Until a larger series, of cases supported by detailed clinical, biochemical and bacteriological investigations, have been studied, conclusions as to the ætiology of chronic nephritis cannot be advanced with confidence.

Dr. W. Cramer said that his contribution to the discussion was a description of an experimental nephritis which was peculiar, in so far as it was completely atoxic —and even Professor Duguid's nephritis could scarcely be called atoxic. It was produced, rather quickly, in rats, by keeping them on synthetic diets from which magnesium salts were excluded. If one gave the animals a synthetic diet and excluded magnesium salts, a nephritis ensued in about six weeks. If magnesium salts were given and calcium was excluded, nothing happened. If both magnesium salts and calcium salts were excluded at the same time, again nothing happened. The pathological condition was therefore clearly due to an imbalance between magnesium and calcium. There was evidence that magnesium and calcium had, in many respects, a biological antagonism. One rather striking example of this, which might have some relation to the condition under discussion, was the effect of magnesium and calcium on the phosphatase of the kidney. The kidney had a ferment which split up organic phosphorus esters into inorganic phosphate, and this ferment was enhanced in its activity by magnesium, and inhibited by calcium.

The condition differed from the nephritis described by Professor Duguid, in that the glomeruli degenerated first and the tubules were affected later, as a secondary effect. If the rats were kept on the magnesium-free diet for about ten weeks there was an extensive fibrosis. During life the animals appeared to be normal; the excretion of the urine was diminished, and there was albuminuria, though the amount of albumin was not high. The animals increased in weight, and while alive showed no difference when compared with the control animals. The kidneys were always enlarged on the magnesium-free diet, sometimes considerably so. The other organs were normal. [The different stages in the glomerular degeneration were illustrated by lantern slides.] Frequently the tufts became attached to the capsule, but there was no proliferation of the capsular epithelium. When stained by the Mallory method, the pictures of the glomeruli resembled those which had been described by Bell for nephritis in man. There was a disappearance of the epithelium, and a thickening of the collagen fibres. The capillaries were often widely dilated, and their number was reduced. In the late stage, the glomeruli were completely degenerated. At first the condition of the tubules was normal, but as the changes in the glomeruli proceeded the tubules gradually degenerated. One feature was that the degeneration always began at the junction between the cortex and the medulla. He (Dr. Cramer) noticed that in Dr. Russell's specimens the healthy glomeruli were also found mainly at the periphery. He did not know why that was so, or what relation the peculiar nephritis he was describing had to the nephritis in man. Obviously, there was practically no possibility of anybody living on a magnesium-free diet, except under abnormal conditions, such as those of war, when vegetables in a fresh state, which were rich in magnesium, were not easily procurable. Under these conditions nephritis had been observed, especially in Germany during the late war.

The puzzling thing was that in nephritis in man, the phosphates were increased in amount in the serum, and the calcium was diminished. In the magnesium-deficiency nephritis the effect was due to the unbalanced presence of calcium, and if the absence of magnesium had any effect on the phosphatase of the kidney, there should be an inhibition of the action of the phosphatase of the kidney on the organic phosphates, and that did not fit in with the increase of phosphates of the serum in

human nephritis. The extraordinarily specific change in the glomerular capillaries suggested that it must have some bearing on the ætiology of nephritis in man. Perhaps a partial, but long-continued, imbalance between calcium and magnesium made the glomeruli more susceptible to the action of toxic agents. He thought it approximated most closely to the nephritis which Dr. Hare had just described as occurring in dogs, in which it was connected with osteoporosis.

Mr. J. G. Wright said that he welcomed Dr. Hare's experience of chronic nephritis in the dog, since there was little on the subject in veterinary literature. Medical literature, on the other hand, abounded with records of the good work done by Dr. Dorothy Russell and others, and veterinary clinicians had had to depend on medical literature for information on the subject. Chronic nephritis was much more frequent in the dog than Dr. Hare had implied, and he (the speaker) considered it one of the commonest causes of death in adult dogs, especially in males.

One point not stressed by Dr. Hare was the very rapid loss of flesh seen in dogs with this disease. In many cases there was a history of insidious disease extending over two or three months, the chief symptoms being increased thirst, occasional vomiting, and polyuria. In others it was evident that the dog was normal a week previously, and that in the meantime it had lost much flesh, this being especially marked about the flanks and the facial muscles, e.g. the temporals. Yet at autopsy fat was found in almost normal amount in the fat-storage parts of the body.

Hypertension in the dog could not be easily estimated by the clinician. The available artery was the femoral, but its subcutaneous course was so short that, as soon as the bandage was applied, the artery was lost. He had made unsuccessful attempts to estimate the pressure by means of the sphygmomanometer.

A further point was that, apart from the cardiovascular changes seen in dogs in chronic nephritis, there was another common form of endocarditis associated with the valves of the dog's heart, in which the sounds were of a continuous and blowing nature. This disease was unassociated with nephritis, and was not often serious.

The urine of the dog in chronic nephritis constantly showed certain features. It was light in colour, and contained small amounts of albumin. Its specific gravity gave the best indication of the extent to which the disease had progressed. Glycosuria in dogs was very rare. Bile and indican were absent in the early stage, but might be present later. Urea excretion was reduced and there was a rise in blood-urea.

A striking difference between the symptoms of chronic nephritis in the dog and those in man was that in the former œdema was absent, possibly because salt excretion remained normal.

Dr. Hare had referred to the condition osteitis fibrosa in dogs, involving the maxillary bones. Twelve months ago, Fish had presented to this Society pathological sections of osteitis fibrosa, but the chief concern was with the parathyroid glands, and the condition was primarily a parathyroid derangement. Both the dogs had had chronic interstitial nephritis, and the speaker had said that this disease was clinically associated with chronic contracted kidney in the dog. Osteodystrophy was not unknown in man in association with post-scarlatinal nephritis.

Another striking difference between glomerular nephritis in the dog and the same condition in man was the rarity with which the acute forms of the condition was seen in the dog. These cases were of insidious onset, and that gave a point of interest as to the ætiology. Livesey had suggested that the cause of chronic nephritis in the dog was canine distemper in early age, but he (the speaker) knew of no evidence to support that view. That opinion gave no explanation of the long period between recovery from distemper and the onset of chronic nephritis, perhaps twelve years later, nor did it explain why males were more commonly affected than

females. Dental sepsis had been said to cause chronic nephritis in dogs, but he (the speaker) disagreed as he had found the mouths of dogs with chronic nephritis to be in good condition; when there was advanced uræmia, however, the mouth was filthy. Medical literature suggested that excess protein in the diet might cause chronic nephritis, but the dog was carnivorous, and here the incidence was not associated with protein diet. Of domestic animals, the cat was a great protein feeder, and in that animal nephritis in any form was rare. Carbohydrates had also been said to cause nephritis in man, and some attributed many diseases in the dog to the eating of dog-biscuits, but there was no evidence for this. Diabetes mellitus, or at all events glycosuria, was also rare in the dog. Abnormal purin metabolism had been said to cause interstitial nephritis. Dogs, however, did not suffer from gout. A further suggested cause of chronic nephritis in the dog was erythematous diseases, to which the dog was very subject, and this might be a point worth investigating. While "cold" could not be said to cause nephritis, he considered that "cold" might cause a chronically diseased kidney to "flare up," and as a result the dog might die within forty-eight hours from uræmia.

It was not possible to cure chronic nephritis in the dog, but the animal's life could be made more comfortable for months,—in some cases for years. Nitrogenous metabolism and exercise should be reduced as much as possible. The diet should contain minimal amounts of protein. Butter, beef-fat, bread, butter and sugar were recommended; vomiting and acidosis were combated with insoluble bismuth salts and salts of potash.

In man attempts had been made to overcome the symptoms of uræmia by provoking diaphoresis; nitrogenous products could be detected in the perspiration. The dog, however, had few sweat-glands.

Dr. E. Stolkind said that he was interested in allergic diseases, but he had not found in the literature any record of a proved case of nephritis due to allergy, and he wondered whether such had been found in animals.

Mr. Wright had mentioned the occurrence of oral sepsis in dogs, and had said that in human beings oral sepsis caused many diseases. When a medical man was baffled as to diagnosis or treatment, he was very apt to declare that oral sepsis was the cause, and to order removal of all the teeth. He (the speaker) had seen some hundreds of such cases, and he had advised many patients to disregard this wholesale order, because he maintained that there was no experimental, pathological, bacteriological, or clinical proof that oral sepsis was a cause of any disease, except in the neighbourhood of the jaws.

Dr. J. T. Edwards said he felt impelled to make one or two observations from the standpoint of a general veterinary pathologist.

He welcomed the remarks of previous speakers for the valuable light they had thrown upon one of the most obscure features of special pathology in many species of animals. Following the searching account given by Dr. Russell of the histogenesis of the most common forms of nephritis in the human species, they had heard the rather remarkable reports given by Professor Duguid and Dr. Cramer upon the induction of peculiar types of chronic nephritis in some species by certain dietary disturbances. This might prove the means of throwing light upon the frequency with which certain forms of chronic nephritis were seen in some species of animals. Until recently, the experimental approach to this study had been extremely difficult, on account of the drastic nature of the agents that had to be employed to set up nephritic conditions in laboratory animals.

He hoped that Dr. Hare would continue the study of chronic nephritis in the

dog. Sir John McFadyean (1929), in a review,[1] mostly of his own long experience upon nephritis in animals, had insisted that the relative frequency of the different recognized forms or types of nephritis in the domesticated animals required further study. Sir John particularly emphasized that when reporting lesions workers should supplement their descriptions with photomicrographs. From his (the speaker's) recollection of routine post-mortem work, chronic interstitial nephritis was extremely common in dogs; it was indeed rare to see an old dog without some degree of this condition in its kidneys. Unlike that of Professor Wright, however, his (the speaker's) impression was that chronic nephritis was also very common in old cats, but the lesion in these animals was of a different kind, namely, a chronic parenchymatous nephritis, with more or less marked fatty changes—the so-called "enlarged white kidney"—in contra-distinction to the "indurated contracted kidney" of the dog. What accounted for the very high frequency of chronic nephritis in these two species of carnivores, and for the different type of nephritis in the two species, one did not know.

In other species of domesticated animals—herbivores and omnivores—nephritis was, on the whole, comparatively rare and, when it was encountered, was usually the direct result of specific bacterial infection. Thus, in equines, pyæmic nephritis was one of the common morbid manifestations of the ætiologically complex condition of pyo-septicæmia of the new-born, known commonly as "joint-ill" of foals. The suppurative foci seen in large numbers in the kidney cortex were commonly found to arise in the type of joint-ill caused by *Bact. viscosum equi*, which was probably a member of the Friedländer group of bacteria. In bovines, on the other hand, there was not uncommonly found in cows a typical pyelonephritis, caused by corynebacteria or diphtheroid bacteria. The clinical disease was often so mild that the condition was not recognized until the apparently normal animal was slaughtered for human food. It was believed to arise after the dystokia and *retentio secundinarium* which occurred so commonly in this species. It was of interest in this connexion to recall the studies recently made by Jones and Little (1925, 1926, 1930)[2] upon the diphtheroids of the genito-urinary tract of calves. They claimed to have found bacterial types normally resident in the outer vestibule, which were potentially capable of giving rise to cystitis and probably pyelonephritis. In sheep, there was a condition known as "pulpy kidney," an acute parenchymatous nephritis of lambs, commonly seen as outbreaks in some territories (New Zealand and Western Australia particularly) and studied recently by Bosworth and Glover[3] at Cambridge. Nothing seemed to be known as to its ætiology. He could not recall any common nephritis of the pig. It was perhaps not unworthy of mention that nephritis, as a local manifestation of a specific generalized infection, might take on different forms or degrees of severity in different species of animals. Thus, in the ox, the lesions of tuberculosis were always relatively slight in the kidneys, whereas in the rabbit, infected experimentally, they were usually very severe. It seemed indeed that in some ways each species of animal was a law to itself with regard to the frequency of disease of the kidneys, the forms which the lesion took when disease did arise, and the causal agents—bacterial or otherwise—which produced the nephritis.

Dr. Dorothy Russell (in reply) said she had been very interested in the accounts of the experimental work which had been done on this subject. She found it difficult to correlate the nephritis described by Professor Duguid and Dr. Cramer with nephritis in man, particularly with regard to the glomerular changes, because,

[1] McFadyean, J., 1929, *Journ. Comp. Path. and Ther.*, xlii, 58-71, 141-162, 231-241.

[2] Jones, F. S., and Little, R. B., *Journ. Exper. Med.*, 1925, xlii, 593-608; *ibid.*, 1926, xliv, 11-30; *ibid.*, 1930, li, 909-920.

[3] Bosworth, T. J., and Glover, R. E. (1931), *Proc. 49th Ann. Congress N.V.M.A.*

unless the glomerular changes observed in Bright's disease in man were accurately reproduced in animal experimentation, no close comparison could be made. The glomerular lesions in Professor Duguid's cases seemed possibly to be ischæmic. As he had found arterial hypertrophy so definitely, and also as he had compared the changes in the kidneys of his rats with senile atrophy in the human—which she regarded as essentially of the ischæmic type—it seemed that some elements of the nephritis that he had produced might be referable to the arterial changes.

She would like to know how Dr. Hare gauged cardiovascular hypertrophy when carrying out post-mortem examinations on dogs; he must take some scale, such as percentage of body-weight, in the animals. Even in human beings that was difficult, because in some there was wasting, in others there was œdema, and dogs varied so greatly in size that a standard must be even more difficult to achieve.

She thought the fact that so many people had compared chronic nephritis in dogs with nephritis repens in the human should be of use in experimental work; it was extraordinary how negative had been attempts to cause Bright's disease in animals. But as chronic nephritis occurred spontaneously in the dog, that fact could be made use of to elucidate the ætiology. Ultimately, she thought, the ætiology would be found to be bacterial. Certainly, diffuse nephritis in man was always bacterial when an ætiological agent could be demonstrated, and was usually streptococcal. It was likely that a bacterial ætiology would also be established for nephritis repens, in view of the close relationship of these two types.

Professor Duguid (in reply) said he agreed with Dr. Russell that the glomerular changes which he showed were precisely those which were usually considered, in human nephritis, as ischæmic changes, but the glomerular changes found in his experimental work must have been primary to arterial changes, because they occurred both earlier and with greater frequency than the arterial changes did. Arterial lesions of this kind were of extreme rarity and, whereas very few of the cases which went on for two or three months failed to show enormous numbers of glomerular changes, one did not expect to find destroyed arterioles before five or six months. There was no question that the last changes in these cases were the arterial ones.

Dr. Hare (in reply) said he did not forget that Professor Wright had spoken about the syndrome of chronic nephritis with osteoporosis at the Central Veterinary Society, after he (Professor Wright) had had the opportunity of studying the speaker's post-mortem reports on some of his cases of the syndrome. On analysing his case records, he found that wasting was not a constant feature, clinically or at autopsy, and that was the reason he had not mentioned it in this discussion. He suggested to Professor Wright that it would be more correct to state that temporal and lumbar wastage was common in chronic nephritis, but was not invariable.

He had been glad to hear Dr. Edwards refer to nephritis in animals other than the dog, and supported his statement that each animal was a law to itself. There were many difficulties in the way of systematic study of nephritis in the animals slaughtered for food. In the horse, chronic nephritis appeared to be remarkably rare, though in foals pyæmic nephritis was not uncommonly found at autopsy.

In reply to Dr. Russell's question as to how he (the speaker) gauged cardiovascular hypertrophy: Formerly, in addition to measuring the heart, he weighed all the organs, but this was of no assistance, because of differences of size, breed, etc. His invariable method now was to make a standard incision of the right and left heart and at a standard site to take caliper measurements of the thickness of right and left ventricle. If the ratio of the right to left was greater than 1 to

2·5, he regarded the left ventricle as thickened, but not for a smaller proportion. The shape of the heart must also be taken into account.

He agreed with Dr. Russell that the dog should prove a valuable experimental animal for the study of the problem of human Bright's disease. Observations on the damage to the kidneys by intoxications of sub-lethal dosage over varying periods of time were particularly advisable. Finally, he wished to acknowledge, with special gratitude to Dr. Dorothy Russell, the assistance he had derived from her Medical Research Council Report on Bright's disease, which had suggested to him (Dr. Hare) that the human nephritis repens was histologically very similar to the chronic idiopathic nephritis of the dog.

Section of Dermatology

President—HENRY MACCORMAC, C.B.E., M.D.

[*February* 15, 1934]

Nævus Unius Lateralis of the Mouth, associated with Multiple Nævi of Various Types.—H. W. BARBER, M.B., M.R.C.P.

Mr. T. B. L., aged 53, was referred to me by a dental surgeon for an opinion on a condition of the left side of the mouth, which the patient thought had been present for more than twenty years. He had consulted numerous medical men without, so far as I know, any definite diagnosis being made.

I could obtain no history of a familial tendency to this condition.

There is a papillomatous nævus (nævus unius lateralis) involving the inner surface of the left cheek and extending downwards along the left side of the soft palate. On the buccal surfaces of both cheeks and on the left side of the lower lip are small pigmented nævi. There are several pigmented moles on the face. On the trunk, back and front, are numerous angeiomata of varying size: some flat pigmented nævi, one keratosis on the back, and another on the right upper arm.

Discussion.—The PRESIDENT said that if he had seen the leukoplakic condition on the buccal mucous membrane alone, he would have been inclined to regard it as an example of lichen planus. While he agreed that the other lesions were of the nævoid type, he would like to know if Dr. Barber included the white patches in this category?

Dr. G. B. DOWLING said that he had never before seen a warty nævus involving the mucous membrane of the mouth, and he thought the condition must be very rare. He would like to know whether any account of such a condition had been published.

Dr. BARBER (in reply) said that he thought that the white patches on the left side of the soft palate, the anterior part of the nævus on the inside of the left cheek, and to a slight extent the inner surface of the right cheek, were due to hyperkeratosis. The nævus probably corresponded to a warty papillomatous nævus unius lateralis, as met with on the skin, in which thickening of the horny layer was a salient feature.

In answer to Dr. Dowling: He had not found a description of this type of nævus occurring on the buccal mucous membrane in the textbooks, but he did not suppose that his case was unique.

Leprosy.—I. MUENDE, M.B.

G. R. G., a married man, aged 38, has spent many years as a missionary in China. He first noticed skin trouble whilst in England in 1927, when he had some brownish circinate patches on the right elbow, which were followed by erythematous spots on the right side of the neck. He was seen by a general practitioner in August, 1927, who did not recognize it as leprosy.

In December 1927, he returned to Malaya, and a few weeks later a generalized erythematous eruption appeared over the body with patches on the face, and this

was correctly diagnosed as leprosy by a Chinese doctor. He left Malaya for Calcutta, and was seen later at a hill station in November 1928, by Dr. R. G. Cochrane, who directed the necessary treatment until March 1930. He then saw Dr. Muir, who gave him, in addition to the usual drugs, potassium iodide in bi-weekly doses of 240 gr. each.

The patient then returned to England in 1930, the condition apparently having cleared up, except for the presence of a few bacilli in the tissue above the eyebrow, although there was no clinical evidence of the disease. There was a little anæsthesia of the right forearm extending down the wrist. He maintained this state until April 1931, when, though he had been having hydnocarpus oil with creosote in the interval, a grouped punctate erythema appeared on the legs and to a more marked extent on the buttocks. This type of eruption extended slowly over the trunk and arms, and six months later patches appeared again on the neck and face. At the same time, patches having a superficial resemblance to pityriasis versicolor appeared over the scapular region. From this time onwards he was given intradermal injections of iodized esters of chaulmoogra, which was changed later for the creosoted hydnocarpus oil.

The condition has shown some progress during the last three months. At present there is an erythematous eruption on the legs and abdomen, with small nodules on the abdomen, and large erythematous patches on the face. He also has large irregular shaped superficial patches resembling pityriasis versicolor on the back.

He has never had marked thickening or tenderness of the ulnar nerve, but still has slight anæsthesia to light touch on the right arm. There is no history of contact with leprous individuals.

Examination of swabs from nasal mucosa showed them to be free from Hansen's bacillus, and I am told by Dr. Cochrane that this examination has always been negative. Tissue scrapings, on the other hand, from the affected skin, show numerous bacilli, and a point which I consider to be of considerable interest is that examination of very superficial scrapings of the "pityriasis versicolor-like" patch on the back reveals the presence of a few bacilli.

Report on histological examination.—The epidermis shows no appreciable pathological change.

In the superficial part of the pars reticularis of the corium, however, there are circumscribed round, oval, and also very elongated foci of closely packed epithelioid cells. These masses are also found in the deeper layers, particularly around hair follicles, and noticeably at the level of the arrectores pilorum. The individual cells in these areas show marked vacuolation, and the Ziehl-Neelsen preparations show the presence of bundles of acid-fast bacilli, chiefly within the large "lepra cells." There is very little tissue reaction around these epithelioid masses, and only a slight degree of dilatation of the lymphatic spaces.

Discussion.—Dr. R. G. COCHRANE said that this case was interesting from more than one point of view. The first was the types of skin lesions which the patient showed. The disease frequently did not run to textbook type in the early stages, and the lesions which the patient showed could readily be mistaken for other skin conditions. In the present case the diagnosis was helped because it was so easy to find the bacilli in the tissues. Frequently there were erythematous lesions which showed no bacilli and there was no anæsthesia, and thus the diagnosis was rendered still more difficult.

The second point of interest about this case was that it showed the almost perfect balance which one frequently saw in cases in the East between the host and the bacillus. In such a case as the present the disease was almost symbiotic, the bacillus living in the body as a parasite. If one could carry out a post-mortem examination in an advanced case, one would almost certainly find bacilli, from bone-marrow outwards, i.e. wherever there was reticulo-endothelial tissue. During all the time that he (the speaker) had seen the patient in this country he had had no reactions, but while in India he had one or two severe reactions.

Further, the case illustrated the fact that often when patients who had been abroad came home to England they soon afterwards had a relapse, due to the cold climate and general conditions at home. So that it was very undesirable to send the patients in such cases home unless they had had a long period of freedom from the disease. The microscopic sections showed that there was practically no tissue reaction to the bacillus, again emphasizing the balance between the body and the bacillus. The bacilli were lying in the epithelioid cells of the skin without producing any reaction.

The case showed also that, in spite of treatment, a relapse might occur. This patient had not been over-treated, as he had none of the usual signs of reaction in that respect. Speaking in a general way, he would say that the outlook for this case was more hopeful than in the average patient with this disease, though he was aware one had to be cautious in giving a prognosis. Unless this man should happen to suffer from a debilitating disease, the speaker did not think there was any great risk of a flare-up. As he became older it was possible the disease would gradually lose its hold on him, though he was probably doomed to retain it in some degree during the whole of his remaining life. The fact that the lesions were now showing a tendency to clear up did not mean that he might not have another relapse. He was now moderately contagious, but the chance of his passing the disease to anyone else in ordinary intercourse was practically negligible. It was not exactly known how leprosy was contracted, but probably it was by close contact. All that seemed to be needed was that precautions similar to those for a tuberculous patient should be observed.

Dr. A. M. H. GRAY asked if Dr. Cochrane would give an indication as to the type of cases in which it was valuable to give iodides. For many years the opinion was that iodide was a deadly drug to give to leprosy patients, especially in nodular cases, as the lesions were found to break down severely afterwards. Lately, however, the iodide vogue seemed to have returned, and he would like to know whether the drug should be given to only one type of case, if so, to what type, and what was the best way of giving the iodides.

Dr. COCHRANE (in reply) said that he belonged to the increasing number who did not think that iodides should ever be given in leprosy. Not long ago iodides were in favour, and Muir used to give 240 grains twice a week with the idea of producing reactions. But these were often very difficult to produce and, if caused, might result in breaking down of foci of the disease, with ensuing dissemination, and in such event it was almost impossible to keep up the patient's general resistance sufficiently to prevent further relapses. He had seen relapses occur after the taking of iodides. The general opinion now was that iodides were contra-indicated.

Case of Hirsuties treated by Ovarian Follicular Hormone—A. D. K. PETERS, M.B.

Dr. Wigley and Dr. Brain kindly sent me this case for treatment at the Western Skin Hospital.

O. B., aged 38, complained of hirsuties which she had had for eighteen years. The growth had become heavier during the last six years.

Her general health was good. Menstrual history $15\frac{5}{28}$, the periods were regular, there was normal loss and no dysmenorrhœa.

The patient married at 25; there have been no pregnancies.

Past history.— ? Mumps. *Family history.*—Ten brothers and sisters. No history of hirsuties in the family.

On examination.—Patient had a feminine physique, but she exhibited a heavy growth of moderately thick, slightly curly hair on the moustache and beard area, inner sides of thigh and upper parts of legs. There was feminine distribution of suprapubic hair. The axillary hair was abundant. The eyebrows were heavily marked, the hair of the scalp was fine in character.

Previous treatment.—Electrolysis.

Treatment by ovarian follicular hormone. (June 20, 1933, a week after onset of period.) Œstriol, i.e. crystalline tri-hydroxy-œstrin, 100 Doisy rat units (approximately equal to 330 international units) were taken by mouth every day for a week.

July 30, 1933.—Normal period.

On July 9 (nineteen days after the administration of œstriol) hairs began to fall out without assistance, from the moustache and beard areas. Patient thought that there was also some loss of hair from the eyebrows and legs. About eight or nine hairs were lost a day, this continued for a while, then the loss gradually decreased and ceased by August 31 (sixty-two days after the administration of œstriol). A normal period occurred during this time.

August 31.—Œstriol, 100 Doisy rat units were taken by mouth every day for a week.

September 18.—Hair began to fall again and continued to do so at the rate of four or five hairs a day for twenty-four days, until October 12. More hairs fell from the beard than from the moustache area. It was noticed that bare oval areas about half an inch in length were left on the chin.

On September 3, two days after the administration of œstriol, the menstrual flow began and was normal, except that it lasted for three instead of for the normal five days.

October 12.—Crude œstrone, i.e. keto-hydroxy-œstrin, 1,000 international units (approximately equal to 303 Doisy rat units) were taken by mouth every day for ten days.

Four days later hairs began to fall out at the rate of two or three a day.

November 24.—Crude œstrone, 2,000 international units, approximately equal to 606 Doisy rat units, were taken by mouth every day for ten days. Two or three hairs a day came out at once and have continued to do so until the end of January. By that time there was still a moderately heavy moustache and excessive hair present on the thighs and legs, but only a few stiff hairs were left on the chin. Patient expressed the opinion that a hair might grow again from a follicle but that there was no further growth after this second hair had fallen in its turn. This is in accordance with the findings of Broster and Vines in some cases of virilism treated by unilateral adrenalectomy.

February 7.—Patient stated that a couple of hairs fell out every two or three days, but that hair was beginning to grow again. She had had no treatment for seventy-three days.

The loss of hair has been estimated by the number found on the patient's face-flannel or in the water after washing her face. The loss of hair has always been greater from the chin than from the upper lip. It will be noticed that an earlier but diminished response occurred after each course of treatment. The patient has had eight menstrual bleedings during the time she has been under observation. The first three were normal in time and extent. The fourth decreased in duration, the fifth, sixth and seventh occurred at three-weekly intervals, the eighth on February 7 was normal.

The œstriol used was theelol, of which one capsule contains 50 Doisy rat units (approximately equal to 165 international units).

The crude œstrone used was menformon, of which one tablet contains 1,000 international units (approximately equal to 333 Doisy rat units).

Œstriol and œstrone are both derivatives of a four-ringed hydrocarbon ($C_{17}H_{12}$); œstriol or tri-hydroxy-œstrin ($C_{18}H_{24}O_3$), is the hydrate of œstrone, which is keto-hydroxy-œstrin ($C_{18}H_{22}O_2$).

The physiological effect of each preparation is said to be the same, but there is a quantitative difference in their strength, which is affected by the form of administration. Œstriol is two to six times more active when given subcutaneously than when given by mouth (Curtis and Doisy). Different investigators disagree about the loss of efficiency of œstrone when given by mouth, but the crude form is

not rendered as relatively impotent as is the pure crystalline preparation. It is said that the crude form of œstrone is only from two to nine times more efficient by subcutaneous injection than by oral administration.

This loss of efficiency of œstrin when taken by mouth is believed to occur in the liver and not through the action of digestive enzymes in the gut. Absorption can also take place through the nasal, vaginal, and rectal mucous membranes, but the most economical method is by injection. The dosage in this case was dictated by economic considerations, the requirements of different patients probably vary enormously as they have been found to do in animals. While small doses may be ineffectual, enormous doses may defeat their own ends by depressing the activity of the anterior pituitary lobe, and so its gonadotropic function. It is obviously absurd to administer œstrin from an external source in such quantities as would cause its diminished production in the body.

That the dosage of 34,620 international units of œstrin, used over a period of six months in this case, was not excessive, is shown by the fact that Kaufmann used 1,000,000 international units to cause the proliferative phase of the endometrium in castrated women.

The time of administration in the menstrual cycle would seem to be important. Frank states that œstrin is present in the blood in greatest amounts on the first day of menstruation, after which it falls abruptly. Siebke states that the greatest amount is present on the fifteenth day, corresponding to ovulation. Usually the administration of œstrin is confined to the first half of the intermenstruum. Administration in the latter half was associated with dysmenorrhœa in two instances in my experience.

This case would appear to be one of endocrine imbalance. When compared with Cushing's syndrome, positive findings are the presence of hirsuties and of erythema reticulatum on the arms and legs and the occurrence of a purpuric eruption on the arms after taking the blood-pressure, which was found to be 140-80. The patient is round-shouldered. Negative findings are the history of no amenorrhœa, no obesity, no polyuria, no backache, no headache or visual disturbances, no liability to bruising. There are no freckles or pigmentation; there are a few striæ on the thighs. When compared with true virilism, positive findings were the hirsuties and heavily marked superciliary ridges; negative findings are the feminine physique, voice and expression, suprapubic distribution of hair, normal menstruation and nature of the breasts. Other findings are a small thyroid and perforated palate.

No biochemical investigations have been made as the patient was not treated at a general hospital.

I have treated five other cases of hirsuties by ovarian follicular hormone. One case sent by Dr. Sibley was very similar to this in appearance. She was given 50 Doisy rat units of œstriol by injection every day for a week. After a fortnight there was a slight loss of hair from the moustache and beard areas. There was a further loss after administration by mouth. Owing to economic considerations and to the slight response obtained, treatment was discontinued.

A case of virilism with menstruation was treated by permission of Dr. Haldin Davis. After daily injections of 50 Doisy rat units of œstriol, loss of hair from the sternum and face occurred in four days. Further treatment was successful, but the patient has now gone abroad.

Three other cases of slight hirsuties were treated without result. One of these patients stated that the hairs could be pulled out more easily after treatment than previously. I do not count this as a positive result, but I notice that Broster and Vines report similar observations after unilateral adrenalectomy in some cases of virilism.

Kaufmann has shown that enormous doses of œstrin are necessary to obtain full therapeutic effects, so possibly failure in these cases was due to insufficient dosage. More vigorous treatment is to be instituted in the case shown to-day.

If permanent treatment is necessary in this case possibly slight dosage will maintain the feminine type of hair once it is re-established.

Trotter has shown that there is practically only a qualitative—and not a quantitative—difference in the hair covering the male and female bodies.

Œstrin has caused the production of female plumage in the cock and capon (Allen).

I have to thank Dr. Alison Macbeth for much advice in the use and administration of œstrone.

Discussion.—Dr. R. T. BRAIN said he thought there was some improvement in this case since he had sent it to Dr. Peters from Charing Cross Hospital; it was complicated by previous treatment by electrolysis. The essential point was that after œstrin had been given, falling of hair occurred, therefore much was to be hoped for when the treatment was thoroughly worked out.

Dr. H. W. BARBER said that he had ordered injections of ovarian extract for cases of hypertrichosis, without success; possibly the dosage had been too small. One case, however, of a different type, was of interest. A young girl had consulted him for what might be called the male type of alopecia, which was not uncommon in females. In disagreement with Sabouraud, he thought that in these cases, as in males, the loss of hair was more evident on the vertex than elsewhere. As a rule, the scalp was excessively greasy, and the hair became progressively thinner. This girl had been losing her hair for four years, menstruation was irregular, and there was slight hypertrichosis on the face. He suggested injections of theelin, and the result was striking, as the hair ceased to fall out and became much less greasy, and after two months there was some regrowth of new hair. The periods had become normal and the patient felt much better in herself.

He had had one case of virilism in a woman whom he found to have a large suprarenal tumour. In addition to the growth of a beard and moustache there was loss of hair on the vertex of the scalp. The tumour was removed, with the result that not only the hair on the face disappeared, but complete regrowth of hair took place on the scalp. Unfortunately the tumour recurred, the symptoms of virilism returned, and the patient died. A similar case had been described by Dr. Gordon Holmes in which operation was completely and permanently successful.

Dr. I. MUENDE said that nine months ago he had seen a girl, of masculine build, who had irregular menstruation, and very marked hirsuties, with a beard and a moustache. He sent her back to her doctor with the recommendation to try theelin. He gave two series of six injections, but there was no result. He would like to hear, from Dr. Peters, how far one might go with these injections, and whether there were any signs indicating that the injections ought to be discontinued.

Dr. AGNES SAVILL said that, just before the War, she had seen one patient who had developed hairs all over the body, as well as on the face, following an acute illness. She did not remember whether the menstrual periods were affected, but the patient had been very ill with pneumonia, after which the abnormal growth of hair all over the body and face had appeared. She was given Loewenthal's capsules of ovo-mammoid, which at that date was the favourite endocrine remedy. The abnormal hair growth then cleared up, but there was, of course, the chance that, with the restoration of the general health, the hairy condition might have cleared up in any case. She (Dr. Savill) had tried many ovarian gland preparations, also mammary gland preparations, in cases of hirsuties, but without success. In most of these cases the menstrual history was normal.

Professor OSCAR GANS (late of Frankfurt) said that he had had success with these remedies in cases in which the condition had lasted twenty years. In the case of a school teacher, aged 20, a wig had to be worn. When her hair began to grow, it was at first colourless, but later it was of the ordinary black colour which she had before. In another case a woman with alopecia areata had loss of her hair for twelve years. It seemed clear

that in these cases there was some endocrine deficiency, and he asked whether in the case under discussion there was any sign of such deficiency.

Dr. ALISON MACBETH said that in a case in which very large doses were given—10,000 to 15,000 international units a day—for short periods, the growth of beard had temporarily been more rapid. A curious feature of this case was that the excretion of testicular hormone was found to be abnormally high, that of œstrin being within normal limits.

Dr. PETERS (in reply) said that the dosage of œstrin used in this case was very minute in comparison with that which had been used to obtain therapeutic results in other conditions. Kaufmann had given a million international units weekly and had obtained growth of a primary hypoplastic uterus after finding that weekly doses of half a million units had had little effect in the same case.

Epidemic of Obscure Ætiology occurring in a Coal Mine in Kent.—G. B. DOWLING, M.D. and R. T. BRAIN M.D.

I was first asked to express an opinion on a group of four of these cases at the end of December 1933. They were all exactly alike, and about sixty cases had appeared within a few weeks, out of a total of about eight hundred miners. Only one mine was affected and in that only the coal-getters and haulage men working near the face; no surface worker was attacked and there were no cases among the wives or families of the miners. The epidemic had begun after Christmas and has continued to the present time though the cases have become fewer recently. Up to date over one hundred miners have been attacked.

Examination of a large number—between fifty and sixty—of these cases at the mine three and a half weeks ago revealed the following salient clinical features :—

(1) There were no constitutional symptoms.

(2) A man who was in otherwise normal health experienced suddenly, while at work, a marked irritation, and within a few hours a widespread eruption of more or less constant distribution developed. This eruption became rather more widespread and more irritable during the succeeding few days, whether the man remained at work or not, and then it began to die down spontaneously. In the case of those who remained at work no remission took place, and most of those who returned to work before the eruption cleared up, promptly relapsed. Others who have returned to work after clearing up completely have also relapsed.

(3) The eruption consisted of closely set punctate lesions involving, in every case, the extensor aspects of the thighs, knees, legs, buttocks and forearms, and in many cases the flexural aspects of the forearms, the waist line, the chest and the back. In almost every case the eruption was most dense on the hairy part of the thighs, knees, buttocks and forearms. The lesions consisted mainly of discrete papules, but so closely set at time as to be almost confluent. Some were almost flat, many were scaly and a certain proportion were capped by a small crust or pustule. About 20% of the cases were complicated by boils, mostly rather small. On the non-hairy parts of the skin such as the abdomen, chest, and back, the lesions were usually small dry papules, rather like papules of the subacute follicular variety of seborrhœic eczema.

It was impossible to say on ocular examination whether all of the lesions were perifollicular, but it was obvious that some of them had this localization, especially the pustular lesions. Direct smears and cultures from the pustules were taken by one of us [R. T. B.] and examined further at the London Hospital.

We are naturally interested to learn the cause of the epidemic which we believe to be unparalleled in the history of coal mining in this country. We assumed: (1) That a toxic cause was out of the question, there being no constitutional

disturbance and no incidence among surface-workers or families. (2) Irritant gases were an improbable cause, since the conjunctivæ and the mucous membranes were never affected, and it was definitely stated that no unusual odour was present in the mine. (3) The condition obviously could not be infectious. (4) It must have some relation to working conditions and something relevant must have occurred between December 24 and December 28 when the mine reopened.

There are certain well-recognized peculiarities about the Kent coal mines which may have some bearing on the question. In the first place, two of them are exceptionally deep (3,000 ft.), and very hot and wet; the third, that in which the epidemic has occurred, is only moderately deep (1,500 to 1,600 ft.), and is quite dry, but owing to certain peculiarities in its construction it is hotter than either of the other two; moreover, ventilation is said to be a matter of considerable difficulty. The mine is also extremely humid, wet- and dry-bulb temperatures are practically identical. The men work without clothes and sweat profusely; on an average they drink about six pints of water during a shift.

In the two wet mines certain cases have cropped up fairly frequently over a long period. They consist of an irritant dermatitis often complicated by pustular infection attacking primarily the lower third or half of the legs. These cases appear to be due to some extent to the slushy condition of the roads and are not found among the miners under consideration, though cases of "prickly heat" have always been fairly common.

It is an interesting fact, but one which may be without any significance, that during the Christmas holidays the ventilation was stopped and the mine was said to be unusually stuffy after the holidays. We have thought of two possibilities: (1) There may be some irritant property in the coal or coal dust in the section which the mine happens to have reached at about Christmas. (2) There might be some micro-organism or fungus capable of attacking the skin under the conditions experienced in the mine.

In order to investigate these possibilities I took a case into hospital and applied coal dust taken from the coal face, subjecting the patient to hot air bathing twice during the period of application—twenty-four hours. The test was completely negative.

Two cases have been seen by Dr. Muende at St. John's Hospital where sections and cultures for fungus and micro-organisms are being made. A section already examined at St. Thomas's Hospital shows only a superficial staphylo-pustule with its subcorneal colony.

In spite of the negative result of the application test, it is obvious that the possibility of an irritant dermatitis cannot be excluded by any experiment which does not imitate exactly the working conditions of the mine. The other possibility appears to be an infection capable of attacking the skin in extreme heat and humidity.

Discussion.—Dr. R. T. BRAIN said that *Staphylococcus aureus* and *S. albus* were found in cultures from scrapings of some of the follicles. In one direct film something like a mycelium with yeast-like spores could be seen. The men said that a fine fungus could be seen hanging from some of the beams, and it was so powdery that it fell off as dust when touched. He thought that a mycotic infection might account for the condition, because on some of the men examined there were scaly patches like seborrhœic dermatitis. On the other hand, these might be areas of lichenification.

He regarded this as an occupational dermatitis, probably due to dust and heat, with some other factor the nature of which he and his colleague could not decide. It might be that the miners had struck a seam which yielded a dust containing fine sharp crystals such as silica. Dr. Prosser White's book described similar conditions due to dust.

Dr. SIBYL HORNER said that though she had not seen this type of eruption, or one of such severity, caused by occupations in factories, she considered that the only explanation was a

combination of extreme humidity and dust. One man had said that the face on which they worked was hard, and that the web-bulb temperature had been very high. It had been suggested that as the work progressed, it took the miners further and further from the sources of ventilation, so that on each successive day they were exposed to higher wet and dry temperatures.

She had now seen the temperature readings of this colliery, and the striking thing was that the dry-bulb and wet-bulb readings were almost identical. The air of the mine must be saturated with moisture, and in factories where this condition obtained, or where there was not more than 10° difference between the wet- and the dry-bulb readings, she had found that workers suffered from excessive sweating. On examining the men a fortnight ago, she found the condition chiefly on the legs and arms, not on the ordinary sweating areas. The workers stated that the perspiration was so profuse that it ran down their legs, and their shoes had to be emptied of the moisture. This, she suggested, accounted for the involvement of the limbs.

Dr. F. A. E. SILCOCK said that he had several similar cases amongst miners from Leicestershire collieries. They were sporadic in nature and averaged about 15 per annum, but probably some patients were treated by their local doctors and he never saw these latter. He had classified them as belonging to the superficial pustular perifolliculitis of Bockhart, usually treated them by frequent baths of weak potassium permanganate and local mild antiseptics.

The Leicestershire mines varied in depth from 900 to 1,200 feet and the temperature averaged about 67° F.

In the Leicestershire cases the eruption occurred generally on the legs and buttocks, on the area covered by the trousers, as well as on the forearms, and even on the nape of the neck. He had not noticed it in the axillæ, probably because the profuse perspiration washed away the coal dust, etc., from that part quickly. He thought it was due to the men frequently rubbing themselves down, when perspiring freely, with their grimy hands and sometimes they took a handful of coal dust and earth and used it like talcum powder to wipe off the sweat, this set up a perifollicular irritation. As they worked in trousers only in Leicestershire mines, these became saturated with coal dust and grime and caused the local eruption on the legs, whereas in the Kent mines, which were hotter, they wore a bathing slip only but had to wipe themselves more frequently in the same manner. The eruption seemed to occur in men from both dry and wet workings, and it did not seem to be infectious in nature, as he had not seen it in other members of the same household, nor had he seen it in men who worked at the pit head and therefore not under such hot and moist conditions.

The PRESIDENT said he thought the condition was an example of miliary impetigo (prickly heat). The high temperature of the coal mines and the habit of rubbing the skin with a handful of dust favoured this variety of staphylococcal infection.

Dr. DOWLING (in reply) said that several of the men had had what they called "prickly heat" from time to time, but the eruption occurred chiefly on the trunk. He thought the President's explanation of the mode of occurrence was probably correct—a combination of profuse sweating and coal dust. This would give rise to irritation of the prominent follicles, and set up the inflammatory reaction found in just those places where the follicles were most highly developed.

Three Cases of Schamberg's Disease.—ROBERT KLABER, M.D.

I.—Dr. N., aged 29. Three months ago, three or four ill-defined but discrete areas were observed on the back of the left thigh, each consisting of an aggregation of bright red points. All of these areas have gradually assumed a more uniform brown colour, though several red punctæ are still present on this light-brown background. Two further areas have recently appeared. All are about 2 centimetres in diameter. There are no subjective symptoms. The lesions extend in line from the upper outer quadrant of the buttock to the external aspect of the middle third of the thigh. This somewhat remarkable distribution, however, does not seem to bear any relation to any nerve or nerve-root distribution. There is no family history of

any similar condition. The performance of a recent biopsy appears to have been followed by the disappearance of much of the pigmentation surrounding the scars.

Report on section from back of thigh.—Unstained section: Shows a deep layer of pale yellow granular pigmentation confined to the corium.

Hæmatoxylin and eosin: Shows an epithelium within normal limits but no melanin can be recognized.

The corium shows, just below the pars papillaris, a uniform œdematous infiltrate of histiocytes and small round cells, with a sharp lower limit, except where it passes further down as a perivascular mantle. No extravasation of red cells seen.

Van Gieson and Weigert's stains: Show no demonstrable changes in the collagenous or elastic tissues.

Potassium ferrocyanide and hydrochloric acid staining: Shows the presence of hæmosiderin particles of varying size, lying within and outside the histiocytes.

II.—F. L., is a wood-working machinist, aged 36.

Ten years ago the left shin first became affected. An area of bright red spots appeared which slowly spread, leaving brown pigmentation in its wake. There has been much irritation (an unusual feature).

Two months ago the right leg first became similarly affected. The original lesion here appeared on an underlying scar, resulting from a previous trauma.

Present condition.—There is now present on the left leg an extensive irregular sheet of brown pigmentation on the postero-internal aspect, with other similar though smaller areas on the outer aspect of the knee. The anterior aspect (or shin) is violaceous with lichenification resulting from constant rubbing of this area. A few cayenne pepper spots are now present on the periphery of these lesions. On the younger lesions, however, on the right leg, several such purpuric punctæ may be recognized. No venous varicosity. Wassermann reaction, negative. No family history.

Report on section from left leg.—Hæmatoxylin and eosin: The appearances are similar to those of the previous case, but here new capillaries are seen lying in the infiltrate, in such numbers as to suggest an angiomatous process. These capillaries show swelling and proliferation and there are marked obliterative changes in the deeper vessels with some extravasation of red cells.

Potassium ferrocyanide and hydrochloric acid staining: Shows the presence of very large numbers of hæmosiderin particles, both large and small, within and outside the histiocytes.

III.—The patient, a woman aged 21, has not been able to come, but I have brought up sections from a biopsy. Her lesions are almost identical in appearance with those in my first case, but they are more diffusely distributed on both lower limbs.

I should like to call attention to the uniformity of the histology in all three cases—a well-defined œdematous infiltrate consisting of histiocytes and small round cells, the former loaded with hæmosiderin. New capillary formation, with obliterative changes, is present, in addition, in the sections from the second case.

Kingery wrote[1] in 1918:—

"The circumscribed capillary proliferation suggests a local angiectatic process through which the circulation is impeded; this, in turn, giving rise to a diapedesis of red cells, followed by their disintegration in the surrounding tissue, and resulting in a pigmentation limited by the extent to which the capillary proliferation progresses."

One might add that the persistence of the hæmosiderin deposit results in permanent pigmentation, thus differing from the eventual disappearance of this substance from the site of an ordinary cutaneous hæmorrhage, or purpuric lesion.

[1] *Journ. Cut. Dis.*, 1918, xxxvi, 166.

This might be plausibly explained by the obliterative changes in the vessels obstructing the export of hæmosiderin.

Discussion.—Dr. A. C. ROXBURGH said he understood that there was not entire unanimity as to these being cases of Schamberg's disease. In the past he had shown several cases of that condition. One was in a girl with widespread lesions on the arms and shoulders; another, in a boy, aged 12 years, who had lesions on the legs. In his view, the present cases were typical examples of Schamberg's disease, both in their clinical appearance and in regard to the hæmosiderin deposit in the tissues.

Dr. DOWLING said he thought the finding of an inflammatory infiltrate in the dermis might be important in distinguishing cases of this disease from varicose pigmentation. Did Dr. Klaber know whether such a dense circumscribed infiltrate was to be seen in varicose pigmentation?

Dr. KLABER (in reply) said that two or three cases of the condition in women had been shown. He had looked up the question of the supposed differential diagnosis of this condition from angioma serpiginosum, which obviously presented some similarities. In the latter, the onset was usually in early childhood, there was a tendency to form circinate patches, an absence of marked pigmentation, and a different histological picture; i.e. no pigment granules, and marked changes in the epidermis. In the present three cases in which the histology was almost uniform, there was no change in the epidermis, and in each there was a substantial quantity of hæmosiderin. His view was that Schamberg's disease was a definite clinico-histological entity, certainly distinct from varicose eczema, though possibly related to angioma serpiginosum.

Post-Arsenical Lichen Planus.—GODFREY BAMBER, M.D.

G. W., aged 47, presented himself with a tertiary syphilide in March 1933. Between then and September he received novarsenobillon, 7·65 grm., together with injections of mercury and a single dose of bismuth at the end.

When he was seen again, in December, the eruption now seen had been present for about two months. It had never been very itchy, and was limited to the trunk and the proximal part of the limbs. The lesions, slightly infiltrated, were mostly oval in shape. The more recent ones were pinkish; the older were dusky red and pigmented. A few looked almost bullous and resembled those seen in erythema multiforme.

On the tongue and the mucous membrane of the cheeks were whitish patches, the latter being more reticulated than is usually seen in leucoplakia.

When seeing the eruption for the first time, I thought that it might be that of pityriasis rosea, modified by the previous administration of arsenic, but after further observation I suggest that it is either a lichenoid eruption following the administration of novarsenobillon, or is lichen planus.

Discussion.—Dr. R. KLABER said that he had seen two similar cases in Vienna last year, each following the administration of novarsenobillon. The question was freely discussed as to whether these were true lichen planus, or a "lichen-planus-like" condition. The lesions were similar to those in the present case, except that the papules on the margin were more definitely flat-topped and shiny.

Dr. W. N. GOLDSMITH said that cases which followed the use of novarsenobillon had a very striking similarity to each other, and if they were merely lichen planus provoked by novarsenobillon, one would expect more often an ordinary and typical lichen planus. The case he best remembered was one in which, as in this case, the diagnosis first made was pityriasis rosea. The eruption began with pink, scaly plaques like pityriasis rosea. Then it became more universal and coalescent and one recognized it as salvarsan dermatitis. As it faded it became more and more like lichen planus. In that intermediate stage there were areas of lichen spinulosus. When it had cleared up it did not appear again, whereas lichen planus was apt to relapse. The lesions on the buccal mucosa were difficult to distinguish from leukoplakia, especially as these cases were known to be syphilitic.

Professor OSCAR GANS said he had seen the development of lichen planus lesions after treatment by salvarsan, and clinically they were typical and could not be distinguished from others. He had seen lichen planus which, at first, seemed to be pityriasis rosea. He thought that the lesions in this case were those of acute lichen planus; pure lichen planus developed later. He had also seen lesions typical of lichen planus following trichophyton infection.

He did not regard what was spoken of as lichen planus as an entity, but thought there were different conditions which could develop into lichen planus. If a patient who was in a favourable condition for the development of such lesions, had lichen planus and was scratched, typical lichen planus appeared in the scratch, but only at the time the condition was developing.

Dr. BAMBER (in reply) said he had never seen in this case the typical papules of lichen planus or lichen spinulosus.

United Services Section

President—Surgeon Captain H. E. R. STEPHENS, O.B.E., R.N.

[*April* 9, 1934]

The Symptom of Vertigo.

By Surgeon Commander J. GORDON DANSON, M.D., M.R.C.P., R.N.

Definition.—What is vertigo? The word itself implies rotation, and indeed the symptom has been well defined as "A sensory disturbance with hallucinations of rotation, either of the patient, of his surroundings, or of both." But as rotation is not always present, even in auditory vertigo, I prefer Russell Brain's definition: "The sensation of a disordered orientation of the body in space." For, as he observes, "The common factor in these hallucinations is the abnormal feeling of spatial disorientation, no matter in what plane they occur." [1]

The structures concerned and their function.—There exists in the mid- and hind-brain a whole system ofg anglia, linked up by the stem of the brain; that is to say the crura cerebri, the pons, and the cerebellar peduncles. In front are the optic thalamus, the corpora quadrigemina, and the geniculate bodies, flanked by the grey corpus striatum; behind is the cerebellum. In the brain-stem are the nuclei of the oculo-motor muscles, the facial, auditory and vestibular nuclei, and, closely adjacent to these, the nuclei of the bulb or medulla. This system of ganglia in the primitive mid- and hind-brain has been thrust back in man into unconsciousness, but there is a definite suzerainty of the dominant and conscious cerebrum above in the regulation of the body's position in space. All these ganglia and nuclei are *en rapport* in the most intimate manner; their interplay is easy and harmonious, and they all take part in the tone and position of the body, both static and kinetic. They are all in touch, in one way or another, with the ear, the eye, and the anterior cornua of the spinal cord. They have two sets of intermediaries between themselves and these outer structures—the red nuclei in front and the nuclei of Deiters behind. We are concerned chiefly with the posterior part of this system, the cerebellum and the nucleus of Deiters, and their afferent vestibular influences.

The cerebellum.—Co-ordination means the maintenance of muscular tone. This is essential for balance or equilibration, and, as Purves-Stewart reminds us, the cerebellum is essentially a co-ordinating centre for equilibration. "It receives its afferent impressions from the skin of those parts on which the body happens to be resting, from the muscles and joints concerned in maintaining our balance, from the muscles of the head and eyes, but, most important of all, from the semicircular canals" [2] via the nucleus of Deiters. It exercises its influence on the limbs of the same side, and that influence passes through the nucleus of Deiters.

The nucleus of Deiters.—This receives afferent impulses from the ear and transmits them to the cerebellum. It receives from and transmits to the spinal cord, and further it has forward connexions with the oculo-motor nuclei, with the opposite nucleus of Deiters, and indeed with all adjacent nuclei. Far and away its most important connexion is the vestibular one, with impulses ascending from Scarpa's ganglion in the vestibular nerve-trunk; i.e. static impulses from the otolith, sending up messages of the head's position in space, and kinetic messages of movement from the semicircular canals.

The vestibule, semicircular canals, and cochlea.—A word on this specialized nerve-ending—the labyrinth. It consists of the semicircular canals and Scarpa's ganglion on the one hand, and of the auditory cochlear nerve-ending and the ganglion spirale on the other. Between them is the vestibule. These run so far together in the eighth nerve-trunk, and part company near their entrance to the pons and medulla. These canals form a sensitive register of stability and equilibrium, and indeed of healthy harmonious comfort. If they are absent there can be no vertigo. When present their range of sensitivity varies enormously among normals. Some people become sick in a train, or in a ship in harbour, or at the suggestion of going to sea, or even when walking from pavement to soft grass or earth. The normal labyrinth can be stimulated experimentally by the rotation test for both ears together, and with the caloric and galvanic tests for each individual organ. When so stimulated, the labyrinths respond by the phenomena of vertigo, nystagmus, forced movements of the head and body, and by what is called mis-pointing. There are varying combinations of these, according to the strength of the stimulus, and the position of the head at the time of testing. It is all a matter of reflexes. The reflex of nystagmus, for instance, reduced to its simplest form, is comparable to a flexor plantar response. If the stimulus for the latter is strong enough, you get wriggling and writhing movements travelling up the trunk. If the stimulus for nystagmus is strong enough, you find head inclinations, forced movements, mis-pointing and vertigo. So that we see the semicircular canals passing on their impulses to Deiters's nucleus, Deiters's nucleus most profoundly impressing the cerebellum and adjacent nuclei, and these, in turn, influencing head and limbs and eyes in the matter of tone and of balance or equilibration.

Vertigo as the physician sees it.—With these preliminary remarks on structure and function, the clinical study of vertigo is vastly simplified. There is a firm ground for logic to exercise itself upon. But even so there are many cases to challenge and defy the diagnostician. No physician forgets that Gower referred 90% of cases of vertigo to disorders of the ear. Nor does he forget that there is a vertigo of the eyes. He should let no case leave his ward without an aural examination, and in the majority of cases an ophthalmic one as well. In any case he must examine the optic discs in all cases of vertigo.

In his general examination the physician will note the age of his patient. In the younger he will inquire as to epilepsy, migraine, disseminated sclerosis, or hysteria. In the older he will think of cardiovascular lesions and arteriosclerosis. He may see evidences of neurasthenia, though his instinct makes him loathe that label as a substitute for diagnosis. As regards hysteria he will be wary, because he knows that vertigo can induce hysteria. Therefore he excludes all other causes before he is reduced to that, and if so reduced, he looks for other indications of hysteria, e.g. deafness, loss of smell, gross anæsthesias, etc. He will be careful with the nervous system, recalling possibilities of intracranial lesions, tumours and cerebral abscesses. In these he will look for focal signs or a rise in intracranial pressure.

Congenital conditions, e.g. Friedreich's ataxia and familial vertigo, and cerebral degenerations like syringobulbia, will not be forgotten, nor inflammations like encephalitis lethargica and the various types of meningitis. Physiological states of vasomotor and endocrine unbalance will run through his mind, e.g. the menopause, the reflex causes of vertigo from the pelvis, bowel, or bladder, and the psychical reflexes, such as anxiety or fear. Blood diseases, notably leukæmia, are possible sources of hæmorrhage and atrophy of labyrinthine nerve-endings. Endocrine and vegetative disorders with their varying degrees of unbalance between sympathetic and parasympathetic, e.g. Addison's disease, diabetes, or a disordered thyroid—all these will be thought of and excluded. Finally he recalls that enormous group of toxic causes of vertigo, be they mineral, vegetable, gaseous, bacterial or metabolic.

Some clinical notes on these disorders.—Epilepsy sometimes has an aura of vertigo. If that precedes the fit, unconsciousness must be established for the diagnosis. The interest of the aura lies in this: epilepsy is almost certainly a cortical brain storm, and it is known that stimulation of the interparietal sulcus causes intense vertigo. May not this explain the cause? Again, latent epilepsy is sometimes brought to light through an acute middle ear; obviously this is a reflex affair and the starting trigger of fits. The use of small doses of quinine helps to diagnose between auditory vertigo and the epileptic aura. Migraine sometimes has an aura of vertigo, but here one notes the slow deliberate march of the aura and the optical and sympathetic upsets. Vertigo sometimes alternates with migrainous attacks. Now migraine is almost certainly due to spasm of the cerebral vessels. We can actually see the spasms in the retinal vessels, and we believe that spasm of the internal auditory arterioles is a fruitful source of vertigo.

Cardiovascular causes: It is well to speak of "dizziness" where there is no objective stagger, "giddiness" when the patient tends to fall, and to reserve vertigo for the paroxysmal manifestations. Sudden cerebral hyperæmia causes dizziness especially on stooping; for instance in tying one's shoe laces. If there is hyperpiesia or arteriosclerosis, as for instance in renal disease, that effect is enhanced. In the cerebral hyperæmia of the menopause we notice the same thing. Sudden anæmia causes giddiness, as in syncope. Sometimes there is premonitory giddiness in older people, before a thrombosis or a stroke. Giddiness with headaches in atheromatous old men is always a danger sign. If there is fixation of the stapes, the local safety valve for pressure is lost in that ear, so that vascular pulsations bear directly on the sensitive labyrinthine cells and make things worse. In organic heart disease, when the heart is beginning to fail, some feel giddy in the morning on rising, that indicates vasomotor failure. Some feel giddy at night when going upstairs; that shows failure of the myocardium. If blood-pressure is low, as in convalescence, there is giddiness. This is also true for the blood diseases. Certain arrhythmias, like the effort syndrome, manifest dizziness or giddiness may be quite severe in the higher grades of heart block—the old Stokes-Adams syndrome for example. Again we see it in paroxysmal tachycardia, in flutter, and in the palpitations of hyperthyroidism. A cathartic purge occasionally induces vertigo, especially in persons with some circulatory disorder. Neurasthenics will tell you that they feel as if their legs were giving way under them, that there is a terrible thumping of the heart, and a lump rising up through their chests into their throats and that they are gasping for breath. This may be menopausal or digestive; more frequently it is from anxiety or fear—the fear of sudden death from what they conceive to be heart disease. They never, however, lose consciousness in these attacks.

Disseminated sclerosis is a disease of the young. Such patients complain frequently of a dizzy swaying, almost certainly pontine in origin—but sometimes they get severe and paroxysmal vertigo in the early stages—the vestibular form of onset which the French describe. These may come to the aural surgeon in the first instance as cases of vertigo, or they may be mistaken for hysteria. The associated signs should help, however—intention tremor, absent abdominal reflex, retrobulbar neuritis or optic atrophy, or an extensor plantar response, etc.

Some of the digestive causes (so called) are really the effects of vertigo—acute gastric and persistent vomiting for instance. Gastro-jejunostomy has been performed before now, and even appendicectomy in such cases.

Intestinal parasites may be a reflex cause, but there may be a toxic element as well. The associated eosinophilia helps one here.

Finally, the group of toxic conditions: Among the drugs tobacco has a high place, and so has alcohol, and among the alkaloids, quinine and salicylates are prominent. The atropine and hyoscine group are fairly notorious, and, among the minerals, one should not forget chronic arsenical poisoning.

In the bacterial group toxins are legion, and so are their foci of infection—teeth, tonsils, sinuses, ears themselves, gall-bladder, appendix, colon, and *B. coli* infections. I would mention one in particular, and that is syphilis, both congenital and acquired. It has a selective action; sometimes it affects the fibres of the eighth nerve—a neuritis—or a labyrinthitis, a gumma of the petrous portion, a meningeal gumma, or a fistula of the external semicircular canal. There is no pain in such cases. Other pairs of nerves may be involved, notably the third. The deafness is bilateral, and may come on as early as the seventh week of the disease.

Herpes zoster, of cranial origin, is sometimes associated with vertigo. Any acute toxic disease may cause this symptom; I would mention mumps as a cause of severe vertigo.

Metabolic disturbance accounts for the giddiness of gout. One sees this in the hypoglycæmia following an overdose of insulin, or even in Addison's disease, where the blood-sugar is also low, but the anæmia and low blood-pressure might, of course, be enough to account for it.

Aural vertigo.—With such reflexions in his mind and in his notes, and possibly some suggestive hints as well, the physician transfers the case to his aural colleague, the report of the optic disc and the Wassermann reaction accompanying it.

The otologist may find obvious causes in the outer and middle ears, e.g. wax, a blocked eustachian tube, nasopharyngeal catarrh—that most fruitful source of vertigo—middle-ear disease, cholesteatomata, mastoiditis, or disease of the mastoid antrum. Further, by watch and tuning fork, he can test the cochlear auditory apparatus, and by means of the rotation test and the caloric and galvanic tests he can measure the sensitivity of the labyrinths, in all requisite dimensions.

Now auditory vertigo has these characteristics, none of them pathognomonic, but together conclusive [1]:—

(*a*) There is a sense of rotation of the patient, or of his surroundings.
(*b*) There is diminished excitability in the semicircular canals, as shown by the caloric tests.
(*c*) It is frequently associated with deafness and tinnitus, i.e. cochlear disturbance.
(*d*) It is associated with nystagmus and a tendency to what is known as forced movements.
(*e*) It is sometimes accompanied by diplopia.
(*f*) If severe, prolonged, or paroxysmal, there will be pallor, sweating, disturbance of the pulse-rate and pressure, nausea and vomiting.
(*g*) Very rarely there is loss of consciousness.
(*h*) In labyrinthine lesions the occiput is tilted towards the shoulder on the affected side.

The matter, however, is not so simple and clear-cut as this. The signs are often atypical. Sometimes there is little loss of sensitivity as indicated by the tests. Occasionally, unconsciousness occurs (Russell Brain). Sometimes the auditory symptoms are wanting. Both labyrinths may be affected in a varying degree and pathological states, e.g. acute inflammation of the middle ear, can modify labyrinthine sensibility to the various tests. Asymmetry between the conditions of the two ears and the resulting heterogenous stimuli should never be lost sight of.

Scott [3] finds that lack of patency of the eustachian tubes and invagination of the tympana, unequal on the two sides, is a most fruitful cause. If both tubes are equally inefficient and both tympanic membranes equally depressed, one finds deafness but not vertigo. If, however, one side is worse than the other, then there is severe vertigo, and the deafness is not noticed. Scott attributes many defective air-landings and many fatal spins to this cause, because vertigo in the air is associated with reflex forced movements. In consequence, a pilot with a blocked eustachian tube thinks he is landing on an even keel when in reality one wing is dipping very noticeably. Scott says that all pilots should be able to inflate both eustachian tubes by swallowing, or by Valsalva, or else give up high altitude flying.

The same thing occurs with sailors in submarines and with divers under high atmospheric pressures.

Scott records the case of a woman with early otosclerosis in one ear, who suddenly had intense vertigo while in a shop. She was thought to be tipsy and sent home in a cab. Scott tried to inflate the affected ear; matters did not improve. When he inflated the eustachian tube on the sound side the patient recovered almost at once; that tube had become temporarily blocked.

Spasm of the tensor tympani or of the stapedius can cause vertigo by disturbing the stapes. When the stapedius is at fault, the facial muscles may twitch and quiver.

A number of troublesome cases occur when there is chronic otitis media, or when a mastoid operation has been performed and everything seems quite well. The patients are subject after a time to giddiness, which is accentuated by walking on a narrow plank or on going aloft. I had such a case in a seaman who refused to go aloft. He was sent into hospital and after exhaustive collaboration between the aural surgeon and myself, we could find no special reason for his giddiness beyond a long-standing chronic right otitis media, now dry. He was sent back to his ship after reassurance, and with the alternative of changing his rating if he did not succeed in going aloft. He declined to do either, and was sent back to hospital and finally invalided. At the time I thought he was trying to get out of the Service but I have since read, in the literature, of many such cases, and it appears that they are genuine enough.

From all this we see that auditory vertigo is most commonly produced, not by diseases in the labyrinth itself, but by stimulation from the neighbourhood without. It may be inflammatory, a matter of pressures, of hyperæmia, ischæmia, or it may be a reflex phenomenon.

The Ménière syndrome.—But suppose no demonstrable lesion is found, and the vertigo is severe and definitely auditory in type, then the vestibule is suspect—the labyrinth, cochlea, or both; then the otologist has to ask himself what is going on in that bony petrous invisible fastness, or again, is the lesion behind the petrous bone, that is to say central and not peripheral. The answer is not always easy. He now finds himself in that perplexing maze known as the Ménière syndrome.

Two things may help to clear his mind at the onset: (*a*) He can compare the labyrinth, which is an invisible and inward nerve-ending, with the outward and visible signs of the retina and optic discs. For instance, he can ask himself if there is such a thing as glaucoma or papillœdema in the labyrinth. A rise of endolymph tension? It is plausible; why not? The venous drainage system from the vestibule is more intimate with the intracranial circulation than is even that of the retina. Again, is there a labyrinthine equivalent of tobacco amblyopia? He notices that spasm occurs in the migrainous retinal vessels. Why not then in the arterioles of the internal auditory vessels? (*b*) He must be struck (indeed he has good reason to be) by the gross vegetative or sympathetic upsets so manifest in severe vertigo. Portmann [4], of Bordeaux, has experimented freely on the question of spasm and stasis of the labyrinthine vessels, by drugs—constrictors and dilators, by pressure upon the vertebral vessels and common carotid, by section of the cervical sympathetic, and by peri-carotid sympatheticotomy. He finds that paroxysmal vertigo can be produced either by stasis and œdema, or by angiospasm and ischæmia in the cochlear and vestibular branches of the auditory vessel, the first producing hyposensitivity and the latter hypersensitivity in the labyrinthine cells—and this he compares ingeniously and convincingly with the digital ischæmia of Raynaud's disease. Either extreme of sensitivity may induce vertigo.

The original Ménière case, which I have taken the trouble to look up, came to autopsy, and a plastic lymph exudate was found, which Scott [3] has convinced himself was a serous meningitis due to acute infective labyrinthitis, where

the drum had not perforated. Before Ménière had found that vertigo originated in the labyrinth itself, the symptom was always looked on as a forerunner of apoplexy.

Hæmorrhages as a cause are very rare. Fraser [5] has found one or two old organized hæmorrhages in cases of leukæmia, and of course we can surmise small hæmorrhages after concussion. In that connexion one should mention those traumatic cases of persistent cerebral contusion—so usual nowadays after motor accidents—with giddiness and headache and loss of concentration and general irritability.

Grading of Ménière's syndrome.—Ménière's syndrome, in its acutest form, consists of paroxysms of vertigo of the auditory type, giddiness, reeling, deafness and tinnitus, with bulbar and sympathetic phenomena, nausea, vomiting, cardiac and pressure changes and cold clammy sweat. The attacks strike the patient down suddenly in a paroxysmal manner, but he is not unconscious. He falls away from the side of the affected ear. Nystagmus, even diplopia, may be seen whilst the paroxysm lasts. Headache and vomiting may persist for some time after the attack, but this is very rare. In practice we see modified editions of the syndrome. Fraser [5] divides it into three degrees:—

(*a*) Apoplectiform, with total deafness at the onset, and loss of vestibular function on the side of the lesion. Causes: Hæmorrhage, purulent labyrinthitis, mumps.

(*b*) Sudden onset, but not complete loss of vestibular response. Causes: Toxic neuritis, herpes, glaucoma.

(*c*) A gradual onset. Causes: Cerebral arteriosclerosis, tumours of the eighth nerve, acquired syphilis, occasionally otosclerosis.

Some of the latter cases may have only a transient giddiness with a tendency to recur. There may be some deafness and tinnitus between the attacks.

As a general rule the vertigo of cerebral lesions is less severe than that in the labyrinth itself. It may be exceptionally severe or very slight in cerebellar abscesses, depending entirely on their position. Any tumour may present vertigo as a symptom, but it is commoner in tumours of the posterior fossa. Tumours in the cerebello-pontine angle may present some nasty attacks, but they are not so sudden or paroxysmal as, say those of labyrinthitis proper. Further they are accompanied with tinnitus and deafness. In vascular cerebral lesions a thrombosis will cause paroxysmal vertigo, whilst in local arteriosclerosis the onset is gradual. A focal lesion affecting Deiters's nucleus would cause paroxysmal vertigo with facial pains due to its proximity to the fifth-nerve nucleus and its roots.

Differential diagnosis between cerebral and peripheral vertigo.—In this short paper I cannot go fully into the differences between central and peripheral lesions. Generally speaking, central lesions present focal signs, and later a rise of intracranial pressure. One finds ocular signs, insensitive cornea, crossed anæsthesias or crossed pareses, hemi-ataxias and the like, and possibly optic neuritis, together with deafness, tinnitus and vertigo in a varying degree, and nystagmus.

This last requires a word of differentiation: A spontaneous rhythmic nystagmus with severe vertigo is presumably peripheral. The nystagmus is mixed, rotary, vertical, or oblique, and is towards the side of the irritative lesion but away from it if the lesion is destructive. Thus, in a case of right acute otitis media irritating the labyrinth the nystagmus is towards the right. Should the labyrinth itself become infected and leptomeningitis set in, then we shall see it reversed. Disturbances of the sympathetic are evident and the deafness is of the perceptive type. The nystagmus soon ceases, because of compensatory efforts from the sound side.

On the other hand, the nystagmus of a central lesion is more often in a single plane, vertical and oblique being characteristic. One often sees such nystagmus in epidemic encephalitis. Vertigo is less paroxysmal. Deafness may or may not be present, and there are few signs of sympathetic upset. The patient falls in the

direction of the quick component of the nystagmus. There is no lessening of the phenomenon here, because compensation does not come into play in central lesions [6]. Dundas Grant advises careful readings with the galvanic tests rather than the caloric, when central lesions, so called, are suspected.

Ocular vertigo.—Some cases of vertigo are ocular in origin. How then can we distinguish auditory from ocular vertigo? In the first place, the usual causes of ocular vertigo are (*a*) low degree of astigmatism, (*b*) a strabismus of paralytic type with false projection of the visual fields and diplopia. (*c*) Anomalies of muscle balance—heterophoria. Now shutting of the affected eye in a paralytic strabismus will stop vertigo; indeed the simplest test is to open and close the eyes. If vertigo is present when the eyes are open and not when they are closed, the vertigo is ocular, not aural. Take the example of the superior rectus muscle. I know of such a case which took months before it was fully tracked down. The patient had to keep his eyes open and look up to obtain the diplopia. If he kept his eyes closed there was no vertigo. If he looked upwards with the sound eye closed, a very unpleasant sensation of false projection was experienced.

The ophthalmic surgeon must first discover the diplopia which occurs on looking up and then decide in which eye it is. In aural vertical nystagmus the patient has vertigo when looking straight ahead, which a patient with a paresed ocular muscle never has. Moreover, diplopia is rare in aural cases. Then one notes in the aural case a distinct erroneous projection in the direction of an object, so that if the patient tries to touch it his hand goes too far in the direction of the object—mis-pointing, with associated tinnitus [6].

Treatment of vertigo.—The first maxim is "Treat the cause"—that is if you can find it, which, as I think I have shown, is sometimes more easily said than done. Take auditory peripheral vertigo first. Luminal is the drug, *par excellence*, one half to one grain t.d.s. Larger doses can be given subcutaneously during an attack. I believe alcoholic injections have been tried in very severe cases, and recently Cairns and Brain [1] have had marked success in five cases by section of the auditory nerve. In eustachian cases inflate by catheter. Some use bougies. Tweedie has used small doses of iodides (one or two grains t.d.s.) very successfully when inflation or dilatation was not permanent in its effect.

In some cases small doses of quinine are very effective. In concussion cases one ninety-sixth of a grain of perchloride of mercury will relieve severe tinnitus and vertigo. Amyl-nitrite may give relief in the giddiness of arteriosclerosis. Iodides are the real sheet anchor in the disease. In the neurotic cases bromides give relief. Then there is the whole group of vasodilators and vasoconstrictors. Adrenalin can be used locally or internally, the nitrites, e.g. mannitol, and the like can be used internally. The belladonna group are useful in sea-sickness—and so on.

In all cases look to the nasopharynx and nasal passages, the sinuses, the tonsils, and the teeth. A skiagram may show an offending unerupted wisdom tooth which is causing vertigo reflexly. Various operations can be carried out on the outer and middle ear; e.g. wax can be cleared away. In acute cases fenestration of the tympanic membrane can be carried out. The ossicles, if fixed, can be removed. Mastoid operations are constantly being performed. Peri-carotid sympatheticotomy may be helpful in cases of angiospasm. In central cases, when tumour or abscess is diagnosed, resort must be had to intracranial surgery. There is a class of case in which neuropathic treatment is essential for success. I remember one such case in which the patient went suddenly deaf, and was so cured. When congratulated on the result by his friends, he promptly went deaf again. Lumbar puncture does good in certain cases, especially if the lateral or pontine cisterns are under pressure. Uncapping the external canal and draining the labyrinth by catgut has been successful in Peter's hands.

Conclusion.—Vertigo is a sensory expression of disordered function, produced in

so many ways from such a variety of afferent impulses, all bearing on the labyrinth, that I make no apology for the broad acres of medicine which I have had to traverse in a rapid and superficial survey.

The immediate stimuli, both reflex and direct, appear to be in the nature of hypo- or hypersensitivity in the affected labyrinth, the result of varying pressures, either circulatory or inflammatory, which cause tension changes in the labyrinthine perilymph and endolymph. Stasis of the arterioles, or spasm of these vessels, determines the onset of vertigo and tinnitus and deafness in a large class of cases. Lesions of the middle ear and eustachian tubes are a fruitful source of trouble. Asymmetry, both ears being affected in a varying degree, should always be considered. The labyrinth is sometimes the direct cause of the disorder and sometimes an incident in the disorder.

Only by a sound knowledge of structure and function, and by close co-operation between the physician, especially the neurologist, and the aural and ophthalmic surgeons is there reasonable hope of success.

REFERENCES

1 Russell Brain, "Discussion on vertigo," *Proceedings*, 1934, xxvii, No. 3.
2 Purves-Stewart, "Diagnosis of nervous diseases," p. 207.
3 Scott, S., "Discussion on vertigo," *Proceedings*, 1929, xxii, 965 (Sect. Otol., 43); *Journ. Laryng. and Otol.*, 1929, xliv.
4 Portmann Georges, "Vasomotor affections of the internal ear," *Proceedings*, 1928, xxi, 1917 (Sect. Otol., 97); *Journ. Laryng. and Otol.*, 1928, xxxviii, 860.
5 Fraser, J. S., "Affections of the labyrinth and eighth nerve in leukæmia," *Journ. Laryng. and Otol.*, 1928, xxxviii.
6 Mackenzie, G. W., "Dizziness due to intracranial lesions, toxæmia and eye conditions," *Nose and Throat Monthly*, 1930, ix.

OTHER WORKS OF REFERENCE

Lawson, L. J., "Some diagnostic conditions when vertigo is a symptom," *Ann. Otol. and Rhinol.*, 1930, xxxix.
McKenzie, D., "Ménière's original case," *Journ. Laryng. and Otol.*, 1924, xxxix.
Foster Moore, "Medical Ophthalmology."
Purves-Stewart, "Intracranial Tumours."

Section of Neurology

President—S. A. Kinnier Wilson, M.D.

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DISCUSSION ON INTRACRANIAL PRESSURE: ITS CLINICAL AND PATHOLOGICAL IMPORTANCE

Mr. Lambert Rogers: The subject under discussion may conveniently be dealt with under two main headings: (1) Intracranial pressure, what this implies and what the factors are which are responsible for its maintenance and variability; and (2) its clinical and pathological importance, considering these two features together because they appear to be closely inter-related.

I would suggest a definition of intracranial pressure as the *thrust per unit area exerted upon the inner surface of the cranial dura mater*, or alternatively, as the stress set up in each unit area of the endocranial layer of the dura mater. Although we have no means in clinical practice of directly measuring this thrust, it is conceivable that there must be an optimum value for the healthy individual, and we may forthwith consider what are the factors responsible for maintaining this and bringing about variations in it.

The thrust upon the inner surface of the dura is the resultant of a number of forces the maximum of which on the positive side is the systolic blood-pressure in the main arteries entering the skull, while on the opposing side is, among other forces, the elasticity of the dura mater itself, a not altogether insignificant factor, as can be seen by the surgeon when carrying out extradural explorations in any of the cranial fossæ, because when detached from the bone in cases in which the intracranial pressure is normal or below this, the dura has a surprising but none the less definite tendency to close down on its contents to a slight extent.

Now, other than blood-vessels, the chief intracranial contents are (*a*) brain substance, and (*b*) intracranial fluids. Of these, brain substance is so compressible that any increase in the transmitted pressure on the inner surface of the dura resulting from even a relatively large increase of cerebral substance, whether normal or neoplastic, must be only slight, unless extremes of volumetric increase are reached but, since water is incompressible, a relatively slight increase in the amount of cerebrospinal fluid within the skull must materially increase the intradural pressure. If the dura contained nothing but blood-vessels and brain substance at atmospheric pressure, the intracranial pressure would be considerably less than the systolic pressure in the circle of Willis, because of the loss in transmission through the substance of the brain, brought about by the compression of this to the limits of its elasticity. If, however, the dura contained nothing but blood-vessels and water, e.g. cerebrospinal fluid, introduced at atmospheric pressure, the intracranial pressure would be approximately equal to that in the circle of Willis because, owing to the incompressibility of water, this pressure would be transmitted directly to the dura. Figures 1 and 2, p. 30, may make this clear. It would appear therefore, that because of its incompressibility, the all-important factor in producing an increase in the intracranial pressure is an increase in the quantity of watery fluid within the skull and it follows that efforts to prevent increased intracranial pressure will probably, with advantage, be directed towards preventing an increase in the quantity of the intracranial cerebrospinal fluid.

Although on the positive side the maximum force contributing to the production of the resultant which we term intracranial pressure, is the systolic blood-pressure in the internal carotid and the vertebral arteries, the resultant pressure is affected less by small variations in systolic blood-pressure than by slight changes in venous pressure, which rapidly bring about an alteration in the quantity of intracranial fluid as represented by cerebrospinal fluid and the intracranial blood content. The effect of an increase of venous pressure is readily demonstrable by slightly compressing the jugular bulbs when a needle connected to a manometer is present in the cisterna magna or in the lumbar pond of cerebrospinal fluid. As soon as the compression begins, an immediate and rapid rise in pressure is indicated by the manometer.

Since changes in posture produce appreciable alteration in the state of the intracranial venous pressure, these also affect the state of the intracranial pressure. This can be readily observed by noting the condition of a bone defect in the skull of an otherwise normal subject (e.g. a defect which has been made when dealing with a cranial injury such as a compound comminuted fracture of

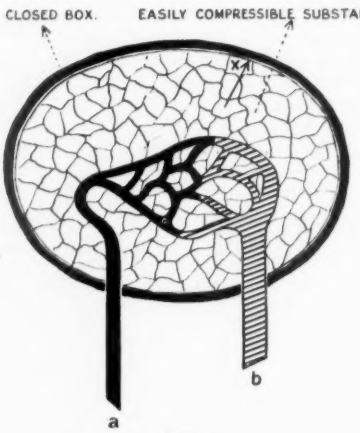


FIG. 1

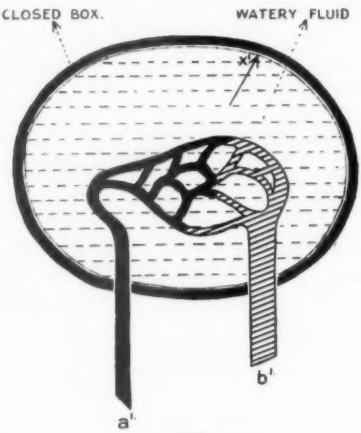


FIG. 2

FIGS. 1 and 2.—Diagrams to illustrate the importance of cerebrospinal fluid in contributing to intracranial pressure. In figure 1 the pressure in the artery, a, transmitted to the spongy substance with which the box is filled, will mostly be expended in compressing the spongy substance to the limits of its elasticity so that the pressure at the point x will be distinctly lower than that in the artery a. In figure 2, however, since the box is filled with water which is incompressible, the pressure at the point x^1 will be approximately equal to that in a^1, there being practically no loss in transmission.

the vault). When the subject of such a cranial defect changes from a lying to a sitting position the soft parts at the bottom of the opening in the skull become increasingly more concave and depressed.

Let us now briefly consider the clinical and pathological importance of this view of intracranial pressure which regards as ill-important the quantity of intracranial fluid. It is well known that the rise in pressure produced by an intracranial tumour is by no means proportional to the size of the tumour, and from the explanation that has been put forward, it can be seen why this is so, since it is not the mass of the tumour which is so important in causing a rise in pressure, but an increase in the quantity of cerebrospinal fluid associated with its presence. It is well known that a large tumour in the frontal region may produce very little rise in intracranial tension, whereas a comparatively small sub-tentorial tumour, by bringing about an

increase in the quantity of intracranial cerebrospinal fluid, may raise the pressure considerably.

It is not proposed to deal with the question of just how the increase of fluid is brought about. It may be due to increased production by the choroid plexuses, to an obstruction to its flow, or to deficient absorption because of a depression of the functional activity of the arachnoid villi, but the all-important point is that an increase in the fluid necessitates an increase in intracranial pressure.

It is known that volatile anæsthetics increase intracranial pressure. This can be demonstrated when a patient with a bone defect in the skull is given an anæsthetic. With ether particularly, the soft parts herniate through the opening in the bone. The pressure also rises during sleep. In each of these instances the rise would appear to be due to an increase either in the quantity of cerebrospinal fluid or of the intracranial blood content, brought about as a result of venous congestion. With this explanation, the rise during sleep, when physiological activity as a whole is slowed and the heart and respiratory rates and the systolic blood-pressure fall, is not so curious as at first sight it may appear. The rise during sleep is no doubt the explanation of the fact that the headache of intracranial tumour is worse on waking than at any other time during the day.

I have referred to an optimum value for the intracranial pressure of the healthy subject. In the upright posture this pressure is somewhere in the region of, or a little below, atmospheric, as can be seen when cisternal puncture is performed with the patient sitting in a chair. The importance of posture has already been indicated. Departures from the optimum pressure, whether on the positive or negative side, and particularly rapid departures therefrom, are manifest clinically by headache.

Because the normal intracranial pressure in the erect position is at—or even a little below—atmospheric, and because the skull is a rigid container, gross defects in the skull itself must at all times keep the intracranial contents at a minimum of atmospheric pressure. Such a condition arising from a relatively large bone defect in the skull appears to be non-physiological and to produce symptoms apart altogether from any manifestations of psychic origin dependent upon the knowledge of the bone defect. It appears reasonable to assume that such symptoms as headache, nausea and feelings of pressure and insecurity, which have been noted in these cases, particularly during and following changes in posture, may arise from the mechanical interference with the conditions necessary for maintaining an optimum intracranial pressure.

For these reasons I believe it is correct procedure to close, preferably by bone-grafting, large cranial defects such as may have been produced by extensive injuries.

It is interesting to turn to the past and notice a record of some experiments performed before the middle of the last century, by Dr. Kellie, of Leith, and reported in a monograph on "Injuries of the Head affecting the Brain," written by G. J. Guthrie, F.R.S. [1], and published in 1842. Guthrie states:—

> "Dr. Kellie, of Leith, bled animals to death under various circumstances; and he found that though all the other organs of the body were blanched and emptied of their blood, the *brain* in these cases presented its ordinary appearance; or even seemed to contain more blood in its superficial vessels than usual. In one instance, he describes the sinuses as being loaded with dark blood, and the vessels of the pia mater as being delicately filled with florid blood. In another, the sinuses were charged with blood, the veins of the pia mater were filled, and the choroid plexuses remarkably turgid. In a very few cases only did he remark that the vessels of the brain contained sensibly less red blood than in others; and in all of these few, some serous effusion was observed. Having satisfied himself by repeated trials upon these points he varied the experiment. He first made a small opening in the skull by means of the trephine, and *then* bled the animals until they died; and in *all these* cases he found that the brain was as completely drained of red blood as any other part of the body."

The results of these old experiments would appear to emphasize the importance of the skull as a closed cavity.

Before considering further the clinical and pathological importance of intracranial pressure, it may be helpful to turn to certain historical aspects, particularly in regard to experimental work. In his "Lectures on Surgery," published in 1824, Sir Astley Cooper [2] states:—

> "I tried the following experiment: I applied the trephine to the cranium of a large dog and took out a portion of bone. I then with the handle of a knife separated the dura mater from the bone; for I found that I could make no impression on the brain until I had done so, and then pressed upon it with my finger. At first the animal did not seem to feel it; but upon pressing more deeply it produced pain and irritation, and he endeavoured to avoid it. Upon still increasing the pressure he became comatose and sunk on the table. I kept him in this state for five or six minutes, when upon removing my finger he got up, turned round two or three times from giddiness, and walked away apparently little worse for the operation. A gentleman who felt the animal's pulse during the continuance of the experiment, stated that it became slower as the pressure was increased."

In 1878, Duret [3] injected wax into the cranial cavity of a dog; respirations ceased. He then incised the occipito-atlantal ligament and opened the cisterna magna, cerebrospinal fluid was ejected with much force and the dog began to breathe again. Two years later, Von Bergmann [4] repeated and confirmed Duret's wax experiment, and also observed the result of compressing a sacral meningocele in a child. The child, at first restless, passed into a deep sleep, while with further compression the respirations at first slowed and became irregular, and the pulse dropped from 120 to 40. Finally a temporary arrest of respiration took place.

Some of the most carefully performed and most complete of the great mass of experimental work dealing with raised intracranial pressure, appears to be that carried out by Sir Victor Horsley and Walter Spencer [5], who in 1892 reported to the Royal Society that:—

> "All the experiments show so clearly that a diminished activity of the medulla occurs as a definite sequence of events contemporaneously with increase in intracranial pressure, that we regard this fundamental fact to be established." They further stated: "Our experiments have an important general bearing, in that they show how the three 'centres' regulating the heart rate, the blood-pressure, and the respiration can be impeded or arrested, either together or almost separately."

It is not proposed to discuss the precise mechanism whereby failure of the medullary centres under the influence of rising intracranial pressure comes about, but it is of clinical significance that the respiratory centre is more vulnerable to pressure than the cardiac centre. Forty years ago, Horsley [6] drew attention to this in a paper, "On the Mode of Death in Cerebral Compression, and its Prevention," and gave it as his opinion that when in cases of intracranial pressure apparent death results, artificial respiration should be immediately performed, and the skull opened freely at once.

It is surprising how well the heart beats are maintained in certain cases of rising intracranial pressure in which respiratory failure has occurred. This clinical phenomenon of a slow, full and strong pulse, with complete failure of respiration, appears to be particularly associated with space-occupying lesions in the posterior cranial fossa, and I have noted its occurrence in cases of hæmorrhage, abscess and tumours situated in this fossa [7]. The logical treatment for the condition is an emergency craniotomy performed upon the posterior fossa, so as to produce a medullary decompression. In a recent case in which this dissociated bulbar failure had occurred and the patient lost consciousness, an emergency operation of this character, carried out without anæsthesia, resulted in her restoration, but I have been able to collect records of a number of cases in which artificial respiration, but no decompression

operation, has been carried out for many hours until those in attendance having at last become exhausted, the respiratory movements have been allowed to lapse and the patient has succumbed.

A further instance of the clinical importance of raised intracranial pressure may be cited. Raised pressure produces a relative deficiency of the intracranial vascular circulation, which as soon as the pressure is lowered is rapidly restored. This must be remembered when operating under general anæsthesia on cases of raised pressure, because any sudden lowering of intracranial pressure, whether by ventricular tap or by opening the dura mater, permits a sudden increase in the blood supply to the bulbar centres, and if not guarded against by previously withholding the anæsthetic this increased blood supply may carry with it an overdose of the particular anæsthetic in use and result in the sudden death of the patient.

Finally, I would draw attention to a still further example of the clinical importance of increased intracranial pressure. Operations performed upon cases in which this is much raised carry with them an appreciable risk; if, however, the tension can be lowered before operation, kept lowered throughout the operation and subsequently maintained at a normal level, this risk is very much lessened. Cases in which the intracranial pressure is normal or slightly lowered offer very little risk, and the operative mortality from such procedures as retrogasserian neurotomy, operations for pituitary tumour when the intracranial pressure is normal, and exploratory craniotomies of all kinds in the presence of normal or lowered tension is low—probably in the region of 1%.

If, following upon the considerations I have placed before you, my contention is correct that the all-important factor in raising the intracranial pressure is increase of intracranial fluid, then it would seem desirable to guard against increase of fluid, especially in cases such as those of intracranial tumour where the initial pressure has already been elevated. For this reason it has for some time been, and is now, my constant practice to drain for a short time most cases of intracranial tumour upon which I operate. Despite any apparent travesty of the principles of neurological surgery as interpreted by the American school of neuro-surgeons, I have found that since adopting drainage there have been fewer post-operative complications, and I have seen no ill-effects, but instead, a quieter and more comfortable convalescence. In most cases the drain is removed in forty-eight hours.

In order to reduce the amount of intracranial cerebrospinal fluid, dehydrators are particularly valuable in cases of raised intracranial pressure, but I believe that gradual and persistent dehydration is preferable to the relatively rapid dehydration which follows the intravenous administration of sugar and saline solutions. A steady lowering of tension can be maintained by the slow administration per rectum, at four or six-hourly intervals, of six ounces of a thirty per cent. solution of magnesium sulphate. For some time we have practised this in the surgical unit at Cardiff in two classes of case, namely, cases of intracranial tumour or abscess, previous to operation; and cases of head injury. In late cases of abscess or tumour, in which through a prolonged state of excessively increased intracranial pressure the patient's condition is poor, it is frequently surprising how much improvement in the general condition takes place in the twenty-four hours following the administration of magnesium sulphate per rectum, and I have known comatose patients, who have appeared to be very bad surgical risks, regain consciousness and improve to such an extent that they have subsequently stood operation well.

Secondly, I have employed this treatment as a routine in all cases of head injury sufficiently severe to necessitate the patient's admission to hospital. The use of dehydration as a routine in cases of head injury has been criticized, largely on the grounds that a sudden lowering of tension may initiate a hæmorrhage or cause bleeding which has ceased to recommence, and also because in certain clinical phases after head injury the cerebrospinal fluid pressure estimated by lumbar puncture is

found to be low. The employment of the rectal solution, however, produces such a gradual reduction of pressure, that it appears most unlikely that this can bring about intracranial hæmorrhage, and since an immediate after-effect of cerebral injury—as of injury to soft parts elsewhere in the body—is a reactionary œdema, the gradual withdrawal of fluid would appear to be desirable. This reactionary œdema appears to take place gradually and to depend in degree and extent upon the severity of the injury. The gradually produced, but persistent, dehydration which the repeated rectal administration brings about would appear to assist reparative changes by gradually withdrawing fluid and thereby lowering pressure, thus allowing a certain amount of actual swelling of the brain to occur. The process is comparable with the incision of the tunica albuginea to allow swelling of the testis to take place after a testicular injury. This decompression or permitted expansion enables reparative processes to take place and saves the testicular parenchyma. If the tunica albuginea is not incised swelling is prevented by this fibrous capsule and testicular atrophy is the result. If fluid is not withdrawn from the skull, cerebral swelling is prevented and a certain degree of pressure atrophy is liable to occur subsequently.

In conclusion I would summarize the main points that have been put forward in this paper as follows: (1) A definition of intracranial pressure; (2) the importance of an increase in intracranial fluid in causing rises in pressure and the reason for this; (3) the desirability of closing large cranial defects because of their interference with the optimum state of intracranial pressure, particularly during changes of posture; (4) the desirability of dehydration before operation on cases of raised intracranial pressure and of drainage afterwards: (5) the desirability of slow continuous dehydration in cases of head injury.

REFERENCES

1 Guthrie, G. J., "Injuries of the head affecting the brain," 1842.
2 Cooper, Sir Astley, "Lectures on the principles and practice of surgery, with additional notes and cases by Frederick Tyrrel, Esq., 1824, vol. i.
3 Duret, H., "Traumatismes Cérébraux," Paris, 1878.
4 Von Bergmann, E., "Die Lehre von den Kopfverletzungen," *Deutsche Chirurgie*, 1880, xxx.
5 Spencer, W., and Horsley, V., "On the changes produced in the circulation and respiration by increase of the intracranial pressure or tension," *Trans. Roy. Soc.*, 1892, clxxxii, 201.
6 Horsley, V., "On the mode of death in cerebral compression and its prevention," *Quart. Med. Journ.*, 1893-4, ii, 305.
7 Rogers, Lambert, "The posterior fossa compression syndrome," *Brit. Med. Journ.*, 1933, ii, 100.

Dr. W. Ritchie Russell: Changes in intracranial pressure are of obvious importance in the study of the effects of head injury, both in the acute and in the later stages. I propose to refer only to conditions which cause changes in intracranial pressure during the acute stage.

Cerebral œdema is well known to be a frequent concomitant of severe cases of head injury. This œdema of the brain produces increased intracranial pressure, so that the brain bulges outwards if exposed at operation. Raised readings may be obtained if the pressure of the cerebrospinal fluid is measured, but these pressure readings are in no way proportional to the degree of unconsciousness present [2]. The pulse-rate provides some indication of changes in intracranial pressure, and it seems reasonable to conclude that the slowing of the pulse-rate, which commonly occurs for a period of a few days following severe injuries, is due to some increase of pressure. In fig. 1 the charts of ten severe but otherwise unselected cases of fracture of the skull have been averaged and recorded in a single chart. Individual cases may, of course, show a degree of slowing of pulse-rate which is considerably more marked than is seen in this graph. This may be prominent even after full recovery of consciousness as in the following case:—

Mrs. L., aged 22, was thrown from the pillion seat of a motor cycle on 30.7.32. She was able to talk a few minutes after the accident, but only became fully conscious twelve hours later. There was a bruise in the right parietal region, bleeding from the right ear, and fracture of the middle fossa was demonstrated by X-ray examination. Slowing of the pulse-

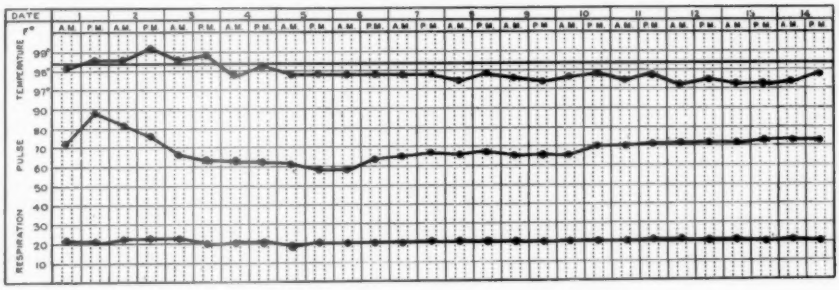


FIG. 1 prepared by averaging the charts of ten severe cases of fracture of the skull.

rate was marked from the fourth to the eleventh day after admission (fig. 2), but during this period the patient was fully conscious and felt well. She complained of numerous dreams during the night, but there was no headache. Slight swelling of the optic discs was present ten days after admission. Recovery thereafter was uneventful and she was quite well eighteen months later.

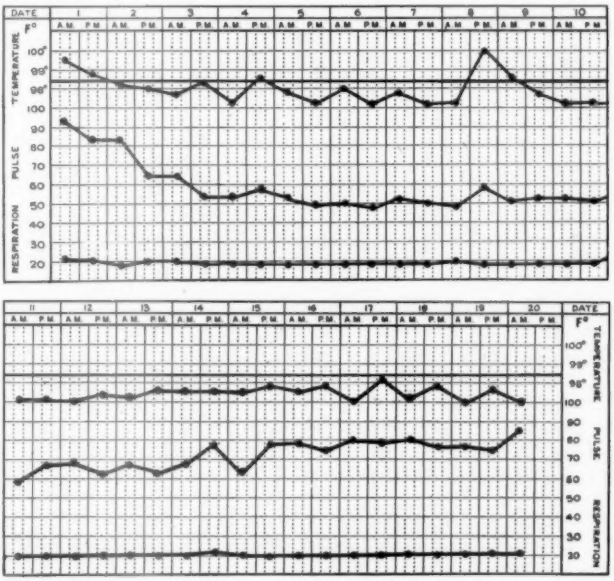


FIG. 2.—Chart of case Mrs. L. showing slowing of the pulse-rate from the fourth to the eleventh day.

Further, it is important to note that dangerous compression of the brain occurs, not infrequently, without the pulse-rate being unduly slow. The unexpectedly rapid pulse-rate in these cases may be due to associated cerebral contusion or to unsuspected injuries of other parts of the body, both of which cause acceleration of

the pulse-rate. Thus a pulse-rate of about 80 per minute may be observed when cerebral compression has reached a critical stage. The following case is instructive from this point of view.

Mrs. R., aged 57, fell downstairs while under the influence of alcohol. Information concerning the degree of subsequent recovery was unreliable, but she was reported to have become unconscious some hours after the accident and was then brought to hospital. When seen twenty hours after the injury, the patient was deeply comatose. The pupils were inactive to light, and the corneal reflex was absent. The skin, however, was warm and dry, and the pulse-wave was strong, the rate being 80 per minute. The respiration rate was 30 per minute, and the temperature was 102·2° F. There was a bruise over the left mastoid and some bleeding from the nose, but none from the ears. Weakness of one side was not demonstrable, but the tendon reflexes were more marked on the right side; the plantar reflex on the same side was extensor, but on the left was flexor. The cerebrospinal fluid was uniformly blood-stained, and its pressure was 350 mm. of water.

In view of the high temperature and rapid respirations and of the fact that there was no slowing of the pulse-rate, it was considered that gross contusion of the brain must be present and that no operation could help. Death occurred a few hours later, about twenty-four hours after the accident. Considerable *contre-coup* bruising of the right hemisphere was found at post-mortem examination, but there was also massive extra-dural hæmorrhage below an extensive fracture of the left side of the middle and posterior fossæ of the skull.

This case might have been relieved by operation, but it presented a difficult problem owing to the lack of reliable information with regard to the degree of recovery of consciousness which occurred following the injury. There are, however, some features of the case which perhaps should have indicated that cerebral compression was the main factor. The strong pulse and the warm dry skin are, I think, important in this connection. Patients dying from cerebral contusion without associated compression by hæmorrhage have, in my experience, a pulse which is feeble and rapid, and the skin is often moist and cold. Further, in such cases I have found the cerebrospinal fluid pressure to be low, whereas in this case it was raised.

In recent years there has been a tendency to consider that œdema of the brain is a critical complication in cases of head injury, and, further, that it leads to those changes in intracranial physiology which cause post-concussional disturbances. On account of this view a line of treatment has developed which aims at removing any œdema which may be present. Frequent spinal drainage, the intravenous injection of hypertonic solutions, and the supporting of the patient in a sitting posture are among the methods now used as a routine in many clinics. My own experience suggests that, in the absence of compression by hæmorrhage, the mode of death of cases of head injury does not in any way indicate that increase of pressure is an important factor. An increasingly rapid respiration and pulse-rate is the rule, and this in itself gives sufficient indication that increase of pressure is not an important factor in causing the fatal result. My own view is that cerebral œdema in itself rarely, if ever, causes a dangerous increase of intracranial pressure.

Is it possible that the cerebral œdema which occurs has a beneficial action in promoting recovery or in preventing complications? The increase of intracranial pressure which it causes can have little effect in controlling gross arterial hæmorrhage, such as may occur in the epidural space, but it must have a great effect in limiting subdural venous hæmorrhage. The intracranial pressure is normally greater than the pressure in the cerebral sinuses, and when the former is increased by œdema of the brain, it seems reasonable to suppose that this increase of pressure will arrest venous hæmorrhage into the subdural space.

With regard to the contention that cerebral œdema in the acute stage leads to the development of post-concussional symptoms, recent experimental work by Rand and Courville [1] does not confirm the view that cerebral œdema leads to excessive glial reaction. I have recently examined a series of 200 cases of head injury at an

interval of eighteen months after discharge from hospital, and only 3·5% of the 200 cases had developed epilepsy, although in none of the cases was intensive dehydration carried out. Further, in this series there were 24 patients who were working men and women under the age of 40, and whose injury had been so severe as to cause loss of consciousness for a period of over three days. Of these 24 severely injured patients, 18 returned to full work within six months of their accident. Cerebral œdema must have been present in many, if not all, of these cases during the acute stage, yet the highly satisfactory recovery-rate does not suggest that it had a damaging effect on the ultimate prognosis.

Therefore, in the absence of any definite evidence that cerebral œdema is harmful in itself, and particularly in view of its action in preventing venous hæmorrhage, it is reasonable to conclude that the use of vigorous methods of reducing intracranial pressure should be avoided, if possible, during the acute stage.

I propose now to refer further to the type of case in which the symptoms and signs of progressive increase of intracranial pressure give cause for anxiety. In such cases increasing depth of unconsciousness and slowing of the pulse-rate are the main causes for alarm. Slowing of the pulse-rate is not in itself an alarming sign, but when it is associated with increasing depth of unconsciousness it becomes a very significant sign of increasing intracranial pressure. For this reason an accurate estimate of the degree of unconsciousness should be made at the earliest opportunity in the management of a case of head injury, so that subsequent changes in the degree of consciousness may be recognized. Careful inquiry for any temporary recovery of consciousness following the injury assumes importance in this connexion. Moderate increases in the degree of unconsciousness do not, however, necessarily indicate serious compression of the brain. I have for example, from a series of 450 cases of head injury personally examined in the acute stage, records of eleven patients who remained fully conscious for a short interval after the injury, but who subsequently passed into a state of confusion for a varying period before recovery of consciousness again occurred. Delayed or continuing subarachnoid hæmorrhage sometimes causes loss of consciousness after an interval of partial, or apparently complete, recovery. The clinical picture which is thus produced may be mistaken for that due to meningitis, because of the accompanying rise of temperature, headache and neck rigidity. The following case illustrates the condition.

D. R., a male, aged 49, fell off a ladder on 18.10.33. He was deeply comatose when admitted to hospital. Two days later he was able to answer questions sensibly, but was slightly dazed, and complained of headache. Two days after this there was a sharp rise of temperature, and the patient became restless and confused. The neck muscles were then found to be very rigid, and Kernig's sign was present. Lumbar puncture showed deeply blood-stained fluid, which contained 800,000 R.B.C. per c.mm. and 8,000 W.B.C. per c.mm. On the day following the temperature had returned to normal and the patient was much more conscious. On this day the cerebrospinal fluid contained 130,000 R.B.C. per c.mm. and 1,400 W.B.C. per c.mm. Recovery thereafter was uneventful.

Delayed subarachnoid hæmorrhage may occur at a longer interval after the injury. Thus a youth aged 17, five weeks after having apparently recovered from a moderately severe head injury, felt a sudden severe pain in the head and rapidly lost consciousness. After admission to hospital, the cerebrospinal fluid was found to contain a large quantity of blood. He recovered rapidly and returned to heavy manual work five weeks after the hæmorrhage. He was in good health when examined twenty-one months later.

In the great majority of cases showing progressive increase of pressure, some evidence develops of hemiparesis owing to the compression of one hemisphere by hæmorrhage. If, in these cases of progressive increase of intracranial pressure, the weakness develops on the side opposite to that on which the skull was injured, then extradural hæmorrhage is the probable cause. There is, however, a possibility of

intracerebral hæmorrhage developing below the site of injury to the skull, and for this reason the surgeon will usually prefer to turn down a bone flap and to open the dura, provided there is no risk of infection from a damaged scalp.

When the side on which the skull has been damaged is obvious, and the hemiparesis develops on the *same* side of the body, this is probably caused by a *contre-coup* injury with hæmorrhage spreading into, or compressing, the hemisphere opposite to the site of the injury. The tearing of pia-arachnoidal vessels is a striking feature of *contre-coup* injury [2], and the resulting hæmorrhage may gradually compress or destroy brain tissue in the neighbourhood. This type of case is not common, but it provides a promising field for surgery.

The following case illustrates this type.

J. S., male, aged 19, was involved in a motor-cycle smash, on 24.9.33. On admission to hospital the same evening he was sufficiently conscious to give his name correctly. When examined the following morning, however, he was deeply comatose. The pupils were

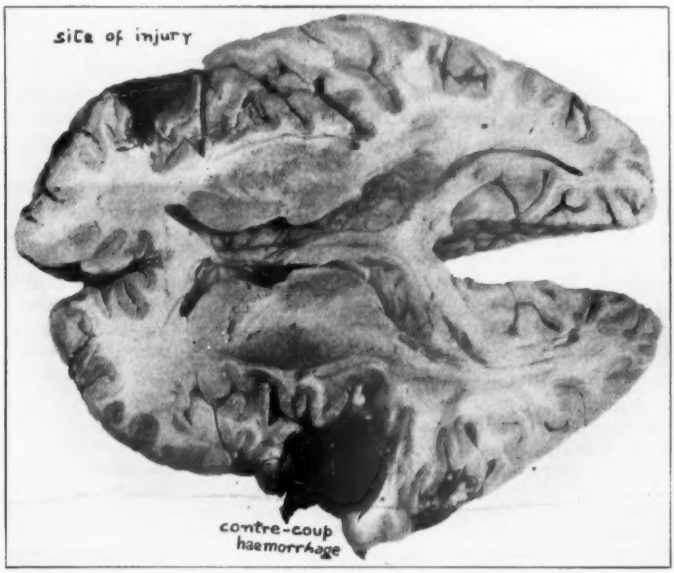


FIG. 3.—Case J. S. showing the contre-coup hæmorrhage which caused hemiparesis.

immobile to light, and the corneal reflexes were absent. The pulse-rate was 70; the respiration rate 20, and the temperature 99° F. There was gross bruising of the scalp in the left frontal and parietal regions, and there was flaccid paralysis of the upper and lower extremity of the same (left) side. It was decided to explore the right side of the brain, but there were a few hours of unavoidable delay, and death occurred at the beginning of the operation. Post-mortem examination showed considerable extradural hæmorrhage below a fracture of the left middle and anterior fossa. On the right side, however, there was a hæmorrhage actually within the Sylvian fissure (see fig. 3) which was presumably the cause of the left hemiplegia. This hæmorrhage, which was hidden within the fissure, was not apparent until the brain had been sectioned. *Contre-coup* hemorrhages are usually, however, clearly visible on the surface of the brain.

In conclusion, I should like again to emphasize that progressive cerebral compression after head injury may be difficult to diagnose if the patient is not fully investigated before becoming comatose. Hence the importance, in all cases, of estimating at the first opportunity the degree of unconsciousness and the presence or absence of hemiparesis. Only by so doing can the subsequent development of compression by hæmorrhage be accurately recognized at a fairly early stage.

I am greatly indebted to the surgical staff of the Edinburgh Royal Infirmary for permission to study the cases of head injury admitted to their wards. The work has been carried out under the auspices of the Statistical Research Department, with the aid of a personal grant from the Medical Research Council.

REFERENCES

1 RAND, C. W. and COURVILLE, C. B., *Arch. Neurol. and Psychiat.*, 1932, xxvii, 1342.
2 RUSSELL, W. RITCHIE, *Brain*, 1932, lv, 549.

Dr. G. W. Pickering: In considering the relationship between intracranial pressure and headache, I shall begin by describing briefly some experiments already published by Dr. Hess and myself[1] on the histamine headache. A bilateral throbbing headache begins about a minute after the intravenous injection of 0·1 mgm. histamine acid phosphate, and lasts about six minutes. We were able to show that the pain is due to a disturbance occurring in the cranial cavity in territory innervated by the fifth cranial nerve. Because the ache is greatly increased by shaking the head, we concluded that it arose from the meninges, and probably from the dura mater, since anatomical evidence suggests that this is the only meningeal structure supplied by the trigeminal nerve. It is well known that the chief action of histamine in man is on the blood-vessels, and the onset of headache is closely related to the vascular events. Histamine produces a fall of blood-pressure and a rise of intracranial pressure which is due to cerebral vasodilatation; headache begins when the blood-pressure has recovered from its fall and when the intracranial pressure is falling from its highest value; it persists when these pressures are normal. The intensity of a developed headache may be modified in two ways. Firstly, a rise of intracranial pressure, produced in a variety of ways, relieves the pain; secondly, a rise of arterial pressure increases the headache and a fall relieves it. It thus seems probable that the pain is due to stretching of a sensitive structure lying close to the meningeal arteries, since it is relieved by a rise of pressure outside these vessels or by a fall within them. Histamine could conceivably produce such a stretching, either by widening the meningeal arteries or by producing œdema of the meninges.

Turning now to pathological headache, the task is more difficult, because there are few facts from which to draw conclusions. It is known that headache is the presenting symptom in a number of diseases in which the intracranial pressure becomes raised, and the most prevalent theory of headache of intracranial origin is that the pain is due to stretching of the parietal dura mater by the raised tension underneath it. In cerebral tumour we know that the intracranial pressure is usually raised, and that some headaches are relieved by the administration of hypertonic solutions which lower intracranial pressure; we also know that headache commonly disappears after operation for decompression. What we do not know is whether in any one individual the intracranial pressure is higher when there is headache than when there is not; and the frequent precipitation of headache by removing cerebrospinal fluid at lumbar puncture makes it extremely doubtful to my mind whether raised pressure is the cause of pain. It must be remembered that the presence of the tumour is associated with other abnormalities in the cranial cavity and one or other of these may conceivably cause pain.

1 *Clin. Sci.*, 1933, i, 77.

In meningitis I have made a few observations not previously reported. If, when headache is present, a few c.c. of cerebrospinal fluid are removed, the pain is relieved, but further withdrawal of fluid increases the pain. Injection of normal saline also increases the pain. There seems to be an optimal pressure (which is within the normal limits of cerebrospinal fluid pressure) at which pain is least; pressures above or below this point increase the pain, but at no point does the headache entirely disappear. The pain of meningitis may possibly be due to a stimulation by the inflammatory process of pain-nerve-endings in the meninges; pressures of cerebrospinal fluid that are either abnormally high or abnormally low may add an additional mechanical deformation of the meninges and so increase the pain.

In high arterial blood-pressure the cerebrospinal fluid pressure may be raised, but headache also occurs in patients in whom the pressure is within normal limits. In each of two patients with raised cerebrospinal fluid pressure I found that the pressures were the same when headache was present as when it was absent, and in both patients the headaches were increased by lumbar puncture.

To sum up: it seems doubtful whether headache of intracranial origin is ever due to a simple rise of intracranial pressure. It seems to me that the cause of the the pain is more probably to be found in some dislocation of the meninges, in an inflammatory condition of the meninges, or in a disturbance of the vasculature.

Finally, in thinking of possible sources of headache, one tends to restrict one's attention to structures that are known to be sensitive. The subject of intracranial sensitivity to pain is in urgent need of careful investigation and is one that would repay the attention of the cranial surgeon.

Section of Physical Medicine

President—M. B. RAY, D.S.O., M.D.

[*March* 16, 1934]

The Composition of Human Perspiration

Samuel Hyde Memorial Lecture

By B. A. McSWINEY, Sc.D., M.B.

ABSTRACT.—Water given off by the skin is classified as insensible and sensible perspiration. Under normal conditions about 600 to 700 c.c. is evaporated from the skin in twenty-four hours. The chief physiological significance of the perspiration is to assist in regulating the body temperature.

The constituents of perspiration are very variable. The average values calculated from the examination of fourteen male specimens and ten female specimens are given below:—

	pH	NH_3-N mgm./100 c.c.	Urea-N mgm./100 c.c.	Amino-acid-N mgm./100 c.c.	Glucose mgm./100 c.c.	Chlorides *g.* NaCl/1,000 c.c.
Average from 10 normal female subjects	6·57	6·0	19·23	6·5	20·0	3·00
Average from 14 normal male subjects	6·14	4·7	21·44	5·0	12·6	3·70

Examination of the figures obtained for the sweat shed by rheumatic subjects shows no marked divergence from those recorded for normal subjects.

Lactic acid is stated to be present in relatively large amounts in sweat, but these results have not been confirmed.

Moss (1923) demonstrated the importance of the loss of chloride which occurred during continued sweating. He showed that symptoms of water-poisoning occurred when men engaged in hard work in hot places drank water freely.

Hancock, Whitehouse and Haldane (1930) point out that the percentage of chloride in sweat increases markedly with duration of sweating, and suggest that water poisoning is due to an alteration in the diffusion pressure of water in the body.

The secretion is under control of the nervous system, and is normally excited through stimulation of the centres by warm blood. The sweat-glands are innervated by fibres of the sympathetic system. Adrenaline has, however, no action on the glands, while pilocarpine excites and atropine paralyses. Recent investigations suggest that acetyl-choline is liberated at the nerve-endings.

RÉSUMÉ.—L'eau excrétée par la peau est classifiée en transpiration insensible et sensible. Normalement 600-700 c.c. s'évaporent par jour. La principale fonction physiologique de la transpiration est le réglage de la température du corps.

Les constituents de la transpiration sont très variables. Les valeurs moyennes, calculées d'après l'examen de la transpiration provenant de 14 hommes et de 10 femmes, sont données ci-dessus (v. résumé anglais).

Un examen des quantités trouvées dans la transpiration de malades rhumatisants ne révèle pas de grandes déviations des chiffres normaux.

On dit que d'assez grandes quantités d'acide lactique existent dans la transpiration, mais ceci n'a pas été confirmé.

Moss (1923) a démontré l'importance de la perte de chlorures pendant la transpiration continue. Il a montré que les symptômes d'empoisonnement par l'eau surviennent chez les hommes qui travaillent exposés à la grande chaleur, et qui boivent beaucoup d'eau.

Hancock, Whitehouse et Haldane (1930) ont montré que la proportion des chlorures dans la transpiration augmente considérablement avec la durée de la transpiration, et suggèrent que l'empoisonnement par l'eau est dû à un changement de la pression de diffusion de l'eau dans le corps.

La sécrétion est contrôlée par le système nerveux, et se produit normalement par la stimulation des centres nerveux par le sang chauffé. Les glandes sudoripares sont innervées par des fibres faisant partie du système sympathique. Toutefois, l'adrénaline n'a pas d'effet sur les glandes, tandis que la pilocarpine les excite et l'atropine les paralyse. Des investigations récentes suggèrent que de l'acétylcholine est libérée au bout des nerfs.

ZUSAMMENFASSUNG: Das durch die Haut ausgeschiedene Wasser ist in sensiblen und insensiblen Schweiss eingeteilt. Normalerweise werden 600-700 c.c. Wasser in 24 Stunden von der Haut abgedämpft. Die hauptsächliche physiologische Bedeutung des Schwitzens liegt in der Regulation der Körpertemperatur.

Die Bestandteile des Schweisses sind sehr veränderlich. Die Mittelwerte, die aus der Untersuchung von 14 männlichen und 10 weiblichen Individuen herausgehen sind in der Tabelle gegeben (s. englische Zusammenfassung).

Die Werte für den Schweiss von Rheumatikern zeigen keine erhebliche Abweichungen von denen für normale Menschen.

Milchsäure soll im Schweiss in relativ grossen Mengen vorhanden sein, doch ist dies nicht bestätigt.

Moss (1923) zeigte die Bedeutung des Chloridverlusts während dem fortwährenden Schwitzen. Er zeigte das Krämpfe bei Männer die schwer arbeiten in einem warmen Ort und viel Wasser trinken vorkommen.

Hancock, Whitehouse und Haldane (1930), weisen darauf hin dass sich mit der Dauer des Schwitzens und dass die Wasservergiftung durch eine Änderung Diffusionsdruck des Wassers im Körper.

Die Schweiss-sekretion ist durch das Nervensystem kontrolliert, und ist normalerweise durch Reizung der Zentren durch warmes Blut ausgelöst. Die Schweissdrüsen sind von Fasern des sympathischen Nervensystems innerviert. Adrenalin hat jedoch kein Einfluss auf die Drüsen, während Pilokarpin sie erregt und Adrenalin sie lähmt. Neue Untersuchungen deuten darauf hin, dass Acetylcholin von den Nervenenden abgeht.

THE composition of perspiration is usually considered to be relatively unimportant, as the chief physiological function of perspiration is to assist in regulating the body temperature by increasing the heat loss by evaporation from the skin, particularly at high temperatures and during muscular exercises. It must be realized however that while the sweat-glands under normal conditions only regulate the composition of the blood-plasma to a minor extent in contrast to the kidneys and lungs, the loss of constituents of the blood-plasma by continued sweating may be considerable.

The work of Moss in 1923 directed attention to the important problem of muscle cramp. He pointed out that with continued sweating a great loss of chlorides occurred, and if the subjects were working in hot places and drinking water freely, symptoms of water-poisoning were brought on. Hancock, Whitehouse and Haldane (1930) showed that the condition of water-poisoning was due to an alteration in the diffusion pressure of water within the body.

Accurate information as to the constituents of perspiration is also important, in view of the use of sweating as a therapeutic measure. While normally small amounts of urea are found in the sweat, it is stated that in uræmia the sweat-glands may assume some of the functions of the kidneys and excrete urea in such amounts that the skin is covered with crystals.

Langley has demonstrated that the sweat-glands are innervated by the fibres of the sympathetic system, yet we have the curious anomaly that drugs which act on this system are without effect, while parasympathetic drugs, pilocarpine and atropine, respectively excite and inhibit. Recent advances in our knowledge of the mode of action of sympathetic and parasympathetic nerves would appear to afford a clue to this apparent contradiction.

Perspiration.—Water is lost from the skin in two ways: by evaporation from the epithelial surface and by secretion through the sweat-glands. When water is evaporated so rapidly that it is not visible, it is termed insensible perspiration. Sensible perspiration occurs when water accumulates on the skin more rapidly than it evaporates.

The term "insensible" perspiration is stated to have been introduced by Sanctorius in the seventeenth century, and it is interesting to note that this physician devised a method, the static chair, by which he could make accurate measurements of body-weight. He discovered that the body is constantly losing weight which cannot be accounted for by the visible excretions. The method of measurement of body-weight is still used to-day as a means for determining the loss of perspiration from the body.

Hancock, Whitehouse, and Haldane (1930) point out that the loss of water by evaporation of water which has permeated through the general surface of the skin, and by evaporation or trickling down of sweat secreted by sweat-glands does not necessary coincide with what is known as insensible and sensible perspiration, for, particularly in dry moving air or air at the low atmospheric pressure of a high altitude, evaporation from the skin is so rapid that when the sweat-glands are secreting actively, or even to their utmost capacity, the general surface of the skin may be dry, so that all the perspiration is "insensible," though far the greater part of it is due to the secretion of sweat. In a hot, dry wind, for instance, the sweat-glands are incapable of keeping the skin moist.

With the first kind of loss by evaporation, it is suggested that the skin is acting as a semi-permeable membrane separating the blood-plasma from the external surface. The membrane is permeable by water but practically impermeable by inorganic salts. For the secretion of sweat the glands are producing a secretion strongly hypotonic in comparison to blood-plasma, but are removing what may be large amounts of sodium chloride from the body. Hancock, Whitehouse, and Haldane suggest that, when the rate of loss of water is small, the loss is entirely due to evaporation of water passing by osmosis through the skin and the small percentage of chloride is derived from epidermis or sebaceous secretion. The potassium lost is far in excess of the sodium. As the loss of water becomes greater, a correspondingly greater proportion is due to true sweating. The proportion of sodium chloride rises while the proportion of loss of potassium chloride to loss of sodium chloride falls gradually.

In the resting condition of the body the temperature of the surrounding air must be raised to about 33° C. before the stimulus to increased activity is evoked.

The following table is of interest as indicating that, at the time of the breaking-out of sweat, the excretion of carbon dioxide by the skin is also suddenly increased, a fact probably related to the increased activity of the sweat-glands (Schierbeck) :—

TABLE I

Temperature of chamber	Water excretion (grm. per hour)	Water excretion (grm. per twenty-four hours)	Carbon dioxide (grm. per hour)	Carbon dioxide (grm. per twenty-four hours)
29·8° C.	22·2	532·8	0·37	8·9
30·4° ,,	27·8	667·2	0·40	9·6
31·5° ,,	71·9	1,725·6	0·37	8·9
31·9° ,,	50·3	1,207·2	0·35	8·4
32·8° ,,	73·4	1,761·6	0·35	8·4
33·8° ,,	82·6	1,982·4	0·87	20·9
35·4° ,,	106·8	2,563·2	1·04	25·0
35·7° ,,	107·0	2,568·0	0·90	21·6
38·4° ,,	158·8	3,811·2	1·23	29·5

Sweat-glands.—The sweat-glands consist of long tubes, of which the secreting part is coiled up into a ball seated at various depths of the corium and in the first layer of the subcutaneous adipose tissue. The excretory duct is continued through the corium, and in a spiral course through the epidermis, opening between two adjacent papillæ, into a large orifice. Although direct evidence is wanting, it is probable, on analogy, that the secretion of these glands is principally, if not

exclusively, the work of cells in its coiled section. The relative distribution of the sweat-glands in man is given as follows: (Luciani)

Forehead	140	Palm of hand ...	310
Cheek	60	Back of hand ...	170
Chest, abdomen ...	225	Sole of foot ...	300
Neck, back, rump ...	50	Back of foot ...	100
Upper arm, leg ...	55 to 70		

Composition of perspiration.—Perspiration is said to represent 25% (600 c.c.) of the total amount of water given off from the body in twenty-four hours under ordinary sedentary conditions. It is described, when collected, as a slightly turbid, almost colourless fluid, salt in taste, and having a more or less rancid smell.

Investigators have found that perspiration consists of water, inorganic salts, ammonia, urea, uric acid, amino-acids, lactic acid and sugar.

An examination of the literature reveals a striking divergence in the observations on the constituents of perspiration. Many investigators have apparently failed to recognize the great variation which exists among individuals, and even in the same individual at different times.

Reaction of perspiration.—Perspiration was held to be alkaline in reaction when shed, but more recent workers report sweat to be acid. Talbert (1919, 1922), Adolph (1926), Mosher (1932). Heuss (1903) states that while sweat is normally acid, on profuse sweating the secretion rapidly passes to a neutral, and finally to an alkaline reaction. This is apparently confirmed by McConnell and Houghton (1923) who found that perspiration becomes more alkaline as sweating continues, and that whilst the range of acidity does not depart greatly from neutrality, it is more often on the alkaline side. Kittsteiner (1913) claimed that the higher the temperature at which the sweat was secreted by the arm, the more acid it became, whilst during secretion over a considerable period (four hours) the sweat gradually approached a neutral reaction. Kittsteiner also claims to have found that the sweat from the arm is more acid than that from the face, whilst that from the legs is almost neutral. Talbert (1922), however, observed the reverse of these results. The work of Vass and McSwiney (1930), which will be referred to later, throws some light upon these conflicting statements.

Chlorides.—The published information relative to the chloride content of sweat varies between comparatively wide limits. Hunt (1912) states that sweat, as it leaves the orifices, never has a greater chloride concentration than 2·0 grm. per litre, such higher concentrations as were recorded being due to evaporation of water.

Kittsteiner (1913) observed in the excretion of the arm a concentration of sodium chloride which ran parallel to the amount of sweat excreted. Adolph (1923) found that the chloride content increased to a marked maximum and then remained constant. Moss (1923) reports a variation from 1·18 to 3·25 grm. per lit., Talbert and Haugen (1927) 4·3 to 8·3 grm. per lit., whilst Barney (1926) recorded a variation of 1·88 to 6·49 grm. per lit., with an average content of 3·10 grm. per lit.

Hancock, Whitehouse, and Haldane consider the variations to be due to methods of collection. When sweat is simply collected from the skin, the concentration of chloride may be too high owing to evaporation, or too low if the wet-bulb temperature of the air is above the temperature of the skin. Or again, the true secretion might be contaminated with salts and other substances on the skin surface.

With increase of the duration and rate of sweating, these observers find that the proportion of chloride removed, or removable, from the skin, to the water given off, increases. At first the sodium chloride may correspond to about 0·1%, but with continued sweating may rise to 0·37%. Even when much water is drunk, the rise in chloride proportion remains high. The normal proportion of potassium chloride to sodium chloride in true sweat is only about 11% and varies very little.

Ammonia, reducing substances, etc.—Variations between 6 and 35 mgm. of ammonia nitrogen per 100 c.c. are recorded, and Talbert, Finkle, and Katsuki (1927) obtained 24 to 112 mgm. urea nitrogen per 100 c.c. Uric acid has been detected in perspiration by a few experimenters, but the amounts vary widely. The presence of creatine and creatinine is still a matter of controversy, and many observers hold that they are not normal constituents. According to Hammarsten and Hedin (1914) sugar may pass into the perspiration of diabetics. Silvers, Forster, and Talbert (1927) found in normal males a variation from 5·6 to 40 mgm. as glucose per 100 c.c. with an average value of 15·0 mgm. Usher and Rabinovitch (1927) obtained in normal individuals a variation of 10 to 27 mgm. per 100 c.c. with an average of 18·0 mgm. and this average was maintained when the subjects were fed with glucose immediately before perspiring. With diabetics these authors found the average value to be somewhat lower, 12 mgm. without, and 13 mgm. after, ingestion of glucose.

Change in the composition of perspiration.—Vass and McSwiney (1930) found that if freshly shed perspiration was allowed to stand at room temperature or at 37° C. the ammonia nitrogen increased considerably and the reaction became definitely alkaline. The glucose content, however, did not disappear, as might have been expected. A typical observation is recorded in Table II.

TABLE II

Date	pH	NH_3-N mgm./100 c.c.	Glucose mgm./100 c.c.	Amino-acid-N mgm./100 c.c.
17.10.29	6·64	6·78	25·4	9·2
Incubated at 37° C. for 72 hours, 31.10.29 ...	8·08	39·0	16·1	3·2

The change in reaction of the fluid and increase in ammonia nitrogen occur gradually, as is shown in Table III.

TABLE III

	Time (hours)	NH_3-N mgm./100 c.c.	pH
Sweat kept in the sterile bottle at 37° C.	0	3·8	5·95
	6	5·0	6·29
	17	12·19	7·0
	24	18·72	7·28
	41	29·96	7·62
	66	37·58	7·7

That the decomposition was mainly accomplished by the bacteria normally present on the skin, which attack the urea and then the epithelial débris, to form ammonia, was demonstrated in the following experiment: The sweat, which had been collected in a sterile bottle (was divided into four portions: (*a*) non-filtered; (*b*) filtered through a filter candle to remove bacteria and also débris; (*c*) non-filtered; (*d*) filtered. The portions (*a*) and (*b*) were kept at 37° C., (*c*) and (*d*) at room temperature. The initial concentration of the urea nitrogen was 18·1 mgm. per 100 c.c. The figures represent the content of ammonia nitrogen per 100 c.c.

TABLE IV

Time in hours	(*a*) Non-filtered at 37° C.	(*b*) Filtered at 37° C.	(*c*) Non-filtered at lab. temp.	(*d*) Filtered at lab. temp.
0	—	—	5·94	—
16	16·5	—	—	—
21	—	5·34	—	5·32
72·5	33·7	—	8·6	—
75·5	—	5·38	—	5·30
117	39	—	14·4	—
147	—	6·76	—	5·86
				Inoculated with a culture of *Staphylococcus albus* obtained from the skin and kept at 37° C. for seventy-six hours.
223	—	7·40	—	16·14

The divergence of opinion recorded in the literature as to hydrogen-ion concentration of perspiration, and ammonia nitrogen, and glucose content of perspiration, can, to some extent at least, be accounted for by the readiness with which perspiration is decomposed even at ordinary temperatures by the bacteria normally present in perspiration. It is clear that unless precautions are taken to prevent decomposition, accurate observations are impossible.

In order to determine the constituents of perspiration, Vass and McSwiney adopted the following method of collection. The subject, who had bathed the previous night, was washed down with distilled water at 98° F., and dried with "sterile" cloths. The rubber suit, which had been carefully washed and dried, was then put on. The suit consisted of four pieces: trousers, jerkin, and two arms fitted with mitts, and perspiration was run off through rubber tubes attached to different parts of the suit.

To promote sweating the subject was placed in a hot room at 103° F., with, as far as possible, constant humidity. A few experiments were made, using a Berthe steam cabinet, a light bath and a radiant heat bath. The length of the experiment varied from fifteen to sixty minutes.

Perspiration of normal males.—Fourteen specimens of freshly shed perspiration from normal males whose ages ranged from 18 to 30 have been examined and the minimum and maximum values obtained from each determination are given in Table V.

TABLE V

	pH	NH_3-N mgm./100 c.c.	Urea-N mgm./100 c.c.	Amino-acid-N mgm./100 c.c.	Glucose mgm./100 c.c.	Chlorides g. NaCl/1,000 c.c.
Minimum values	5·1	2·55	11·10	2·4	9·4	2·65
Maximum values	7·35	7·0	32·92	9·2	26·4	5·01

The fact that considerable variations were observed in the analyses of sweat of different individuals led us to investigate the variations of the concentrations of the constituents of sweat shed by the same individual on different occasions over a long period. In Table VI are shown the minimum and maximum values observed in the analyses of seven freshly-shed samples from the same subject.

TABLE VI

	pH	NH_3-N mgm./100 c.c.	Urea-N mgm./100 c.c.	Amino-acid-N mgm./100 c.c.	Glucose mgm./100 c.c.	Chlorides g. NaCl/1,000 c.c.
Minimum values	5·10	3·8	15·64	4·5	7·3	2·34
Maximum values	6·20	7·0	33·95	9·9	20·7	4·63

The values observed for each determination have been averaged and are compared in Table VII with the average values calculated from the results obtained for the fourteen male specimens. There is good agreement between the averages of the individual's perspiration and those deduced from sweat collected from fourteen male subjects.

TABLE VII

	pH	NH_3-N mgm./100 c.c.	Urea-N mgm./100 c.c.	Amino-acid-N mgm./100 c.c.	Glucose mgm./100 c.c.	Chlorides g. NaCl/ 1,000 c.c.
Average from individual's sweat	5·71	4·8	23·57	7·2	12·7	3·39
Average value for normal males	6·14	4·7	21·44	5·0	12·6	3·70

In Table VIII the average values calculated for the sweat of ten normal females are compared with those obtained for normal males. There is, it will be observed, good agreement between these averages, except in the glucose content.

TABLE VIII

	pH	NH_3-N mgm./100 c.c.	Urea-N mgm./100 c.c.	Amino-acid-N mgm./100 c.c.	Glucose mgm./100 c.c.	Chlorides g. NaCl/1,000 c.c.
Average from 10 normal female subjects	6·57	6·0	19·23	6·5	20·0	3·00
Average from 14 normal male subjects	6·14	4·7	21·44	5·0	12·6	3·70

Sweat collected from stout healthy subjects was found to have a considerably higher glucose content than that from normal subjects: 45, 44 and 43 mgm. per 100 c.c. were obtained from three subjects respectively as compared with 20 mgm.

Rheumatic subjects.—As it has been suggested that the perspiration from rheumatic patients differs from that obtained from normal individuals, a series of analyses had been made of the sweat shed by seven female rheumatic subjects whose weights ranged from 102 to 45 kg. These observations are tabulated in Table IX and compared with the averages for normal female perspiration.

TABLE IX

Wt. (kg.)	pH	NH_3-N mgm./100 c.c.	Urea-N mgm./100 c.c.	Amino-acid-N mgm./100 c.c.	Glucose mgm./100 c.c.	Chlorides g. NaCl/1,000 c.c.
101·8	5·33	—	—	—	42·4	—
101·8	5·85	5·4	26·4	—	24·2	—
98·4	5·89	3·1	17·34	—	22·5	3·81
90	6·56	11·2	10·2	—	23·4	4·04
73	5·8	7·7	12·1	4·0	17·0	3·00
45·5	5·79	2·7	26·14	4·4	14·0	4·05
50	7·76	—	—	—	—	4·38
Average for normal women	6·57	6·0	19·23	6·5	20·0	3·00

An examination of the results shows no marked divergence from the results already recorded for normal individuals, with one exception—the reaction of the perspiration of the rheumatic subjects was acid. Further support is also forthcoming for the finding that the sweat of stout females has a higher glucose content than is found in the perspiration of normal females of average weight. It is interesting to note that only small amounts of sweat could be collected from these subjects.

It will be seen from these results that the reaction of freshly shed perspiration is definitely acid, and the observations recorded agree well with those recently obtained by Mosher (1932).

The chloride or salt concentrations are appreciably less than those reported by most other observers and are comparable with the results of Moss (1923), Barney (1926), though greater than those recorded by Hancock, Whitehouse, and Haldane (1930).

The ammonia nitrogen was found to vary between comparatively narrow limits, but its concentration rapidly increased if the perspiration was allowed to stand. Much wider fluctuations were recorded in the urea nitrogen content. Traces of creatine and creatinine have been found, but were not present in measurable amounts.

Mosher found lactic acid in concentrations varying from 34 mgm. to 107 mgm. per 100 c.c. of sweat, and Talbert states that the average individual's perspiration contains 71 mgm. to 160 mgm. per 100 c.c. The amount is described as increasing rapidly as the result of exercise and Kosiakina and Kristownikoff found 1,765 mgm. of lactic acid per 100 c.c. in the sweat of marathon runners.

Pemberton (1929) gives the following summary of the range of lactic acid found in the sweat of arthritic patients and normal persons:—

Normal persons.—Blood from 14 to 25 mgm. per 100 c.c. Urine 5 to 13 mgm. per 100 c.c. Sweat from 120 to 425 mgm. per 100 c.c.

Arthritic patients—Blood from 11 to 30 mgm. per 100 c.c. Urine from 3 to 21 mgm. per hour from 8 to 31 mgm. per 100 c.c. Sweat from 90 to 458 mgm. per 100 c.c.

Pemberton concludes: (1) That lactic acid is not present in abnormal amounts in the arthritic patient. (2) That as lactic acid is present in sweat in considerable amounts, its presence may be referable to the chemical changes occurring in the sweat-glands during activity. (3) That the benefit accruing to arthritic patients

from sweating measures cannot, in the light of these results, be ascribed to the elimination of lactic acid in the sweat.

Vass has attempted to isolate hydroxy acids from sweat collected from seven normal individuals, but his attempts have proved unsuccessful. Lactic acid, according to his determinations, was not present in amounts greater than 120 mgm. per 100 c.c. of sweat.

It is clear that the sweat-glands are incapable of playing any serious part under normal conditions in the regulation of the level of blood urea. If 600 to 700 c.c. of perspiration are shed in twenty-four hours approximately 0·1 grm. of urea would be removed from the body. After severe exercise the constituents are stated to be increased, and 0·89 grm. of urea has been obtained in twenty-four hours. During the same period approximately 30 grm. of urea are eliminated in the urine. Sweating is therefore not of much assistance in regulating the level of the blood urea in the normal individual. The amount of urea in sweat would require to be increased enormously before sweating could be considered a useful therapeutic measure.

At the same time the sweat is formed from the blood-plasma, and considerable loss of water and salts may occur with continued sweating. Hancock, Whitehouse, and Haldane (1930) suggest that the diffusion pressure of water is normally kept constant by two mechanisms. In the first place, a solution practically isotonic with the blood-plasma is, if no water is drunk, absorbed from the surrounding tissue. The volume and hæmoglobin percentage are therefore not appreciably altered. In the second place, the excess of salt in the blood-plasma, which would tend to be produced by replacing a hypotonic by an isotonic solution, is almost entirely eliminated by the action of the kidneys in excreting urine more concentrated in salts, or more scanty. If, however, as much water is drunk as is lost by sweating, the kidneys will adjust matters by secreting urine containing sufficiently less sodium chloride than does blood-plasma, to balance the loss of sodium chloride in the sweat. If the kidneys are practically out of action, as during hard muscular exertion, the diffusion pressure of water can still be kept normal if just as much water is drunk during the sweating as will so dilute the salt solution absorbed from the tissues that no rise in the percentage of salt in the blood occurs. If, however, too much water is drunk, in response to thirst, with the kidneys still out of action, the pathological symptoms associated with water-poisoning may be produced either in the common form as undue fatigue, etc., or the acute form as cramp.

Innervation.—Goltz, in 1875, discovered that excitation of the peripheral end of the divided sciatic causes the appearance of beads of perspiration on the hairless pads of the cat's feet. It was shown a few years later that excitation of the abdominal sympathetic cord produced the same effect, and that even after ligation of the aorta, sweat was still secreted after excitation of the appropriate nerves, and finally, injection of atropine completely annulled the effects of such excitation. In human beings it is known that profuse sweating may accompany a pallid skin—as in nausea—while the flushed skin of fever is characterized by the absence of perspiration. There seems to be no doubt that the sweat-nerves are genuinely secretory nerves, causing a secretion in consequence of a direct action on the cells of the sweat-glands. According to Langley, the secretory nerves run entirely in the sympathetic system. The pre-ganglionic fibres take origin from the second dorsal to the third or fourth lumbar nerves and pass into the sympathetic chain. The post-ganglionic fibres pass from the cells and are distributed to the whole surface of the skin with the various spinal nerves.

Interesting evidence for the existence of inhibitory fibres for sweat secretion has been put forward by Ott. It is stated that there is immediate cessation of secretion previously evoked by pilocarpine, on excitation of the peripheral end of the divided sciatic. Again, it is said that irritation of the abdominal sympathetic causes a dryness of the pads of the foot on the side of the irritation and that pilocarpine

accentuates this difference between the foot on the side of the irritation and the normal foot on the opposite side. Finally, division of the abdominal sympathetic produces moist pads on the side of the section and the injection of pilocarpine makes these pads sweat before the others.

Spinal centres have been postulated because, when the medulla is separated from the cord by a section in the cervical or thoracic region, the action of dyspnœa or of various sudorific drugs supposed to act on the central nervous system may still cause a secretion. In view of recent work, it is probable that these centres represent the nuclei of origin of the nerves and that the general regulating centre is situated in the hypothalamus.

The nervous mechanism of perspiration may be called into action by central stimuli, by reflex action, or by peripheral stimuli. It is interesting to note that a venous condition of the blood is one of the most active stimuli.

Raising the temperature of the blood produces a similar effect and the result is also obtained with divided posterior roots and is therefore not reflex. The effect is prevented by section of the efferent nerve, so that it cannot be of peripheral origin.

Pilocarpine acts as a peripheral excitant, while atropine is antagonistic to pilocarpine. Certain drugs, such as picrotoxin, appear to act centrally. Eserine is stated to be mainly a central stimulant, but it is probable that on further investigation it will be found also to exercise a powerful influence on the peripheral mechanism.

It is important to remember that the peripheral mechanism is very sensitive to changes of temperature, since not only cold, but also excessive heat, retards the secretion. If one hand be held in water at 45° to 50°C. for ten minutes while the other is immersed in water at 15° to 30°C. and exercise is then taken, the hand which was in water at the lower temperature begins to sweat at once, the other not for a considerable time.

Evidence obtained from recent investigations on the autonomic nervous system suggests that impulses in the sympathetic and parasympathetic nerves are chemically transmitted by substances liberated at the nerve-endings, which act on the effector structure. Acetyl-choline is held to be the substance responsible for transmitting the effect of impulses in the peripheral parasympathetic fibres and adrenaline, or a substance closely related to adrenaline, for transmission in sympathetic fibres.

Acetyl-choline is suggested to be the chemical parasympathetic transmitter, for the following reasons:—

(1) The effects obtained on addition or injection of acetyl-choline are similar to those recorded on stimulation of the parasympathetic fibres.

(2) The action of acetyl-choline and of the parasympathetic fibres is inhibited by atropine.

(3) The action of acetyl-choline and of the parasympathetic nerves is intensified by eserine, which is known to delay the destruction of acetyl-choline.

(4) On stimulation of parasympathetic nerves there is evidence of a substance in the perfusion fluid, or in the venous blood, which has all the properties of acetyl-choline.

Dale (1933) points out that the correspondence between anatomical origin and functional chemistry is not exact. The production of sweat secretion—the contraction of the stomach—sympathetic vasodilatation—are some of the examples of effects produced by fibres which are anatomically sympathetic, but the impulses are apparently transmitted by something like acetyl-choline.

Euler and Gaddum in 1931 showed that stimulation of the cervical sympathetic produces the pseudomotor contracture of the lip after section of the motor nerve. The contracture, they suggest, is due to liberation of acetyl-choline by the nerve-endings of the vasodilators. Harrison and McSwiney (1933) have been able to demonstrate that the contraction of the stomach obtained on stimulation of the vagus or sympathetic nerves is intensified after injection of eserine and inhibited after

injection of atropine. Again, Feldberg, Minz, and Tsudzimura (1933) have advanced evidence to show that the chemical transmitter of splanchnic action on the suprarenal medulla has in all respects the properties of an unstable choline ester.

Dale (1933) suggests the use of the words "adrenergic" and "cholinergic" which will indicate action by two kinds of chemical transmission, due in one case to a substance like adrenaline, in the other to a substance like acetyl-choline. As the sweat-glands are acted on by parasympathetic drugs and are not affected by adrenaline, it seems logical to suggest that the sympathetic fibres which innervate the sweat-glands are cholinergic in function.

BIBLIOGRAPHY

ADOLPH, E. F., *Amer. Journ., Physiol.*, 1923, lxvi, 445.
BARNEY, R. E., *Journ. Amer. Med. Assoc.*, 1926, lxxxvii, 1827.
CAMERER, W., *Zeit. f. Biol.*, 1901, xli, 271.
DALE, H. H., *Journ. Physiol.*, 1933, lxxx, 10 P.
EULER, V. S., and GADDUM, J. H., *ibid.*, 1931, lxxiii, 54.
FELDBERG, W., MINZ, B., and TSUDZIMURA, H., *ibid.*, 1933, lxxx, 15 P.
HAMMERSTEN, O., and HEDIN, S. G., *Physiological Chem.*, 7th ed., New York, 1914, 847, 849.
HANCOCK, W., WHITEHOUSE, A. G. R., and HALDANE, J. S., *Proc. Roy. Soc. B.*, 1930, cv, 43.
HARRISON, J. S., and MCSWINEY, B. A., 1933, unpublished communication.
HEUSS, E., quoted by TALBERT, G. A., *Amer. Journ. Physiol.*, 1919, l, 433.
HUNT, E. H., *Journ. Hygiene*, 1913, lxxiii, 275.
KITTSTEINER, C., *Arch. f. Hygiene*, 1913, lxxviii, 275.
KOSIAKIANA, A. F., and KRISTOWNIKOFF, A. N., *Arbeitsphysiol.*, 1930, ii, 421.
LUCIANI, L., "Human physiology," London, 1913, ii, 485, 486.
MCCONNELL, W. J., and HOUGHTON, F. C , *Amer. Soc. Heat and Vent. Wash.*, 1923.
MOSHER, H. H., *Journ. Biol. Chem.*, 1932, xcix, 781.
MOSS, K. N., *Proc. Roy. Soc. B.*, 1923, xcv, 181.
OTT, I., *Journ. Physiol.*, 1879, ii, 42.
PEMBERTON, R., Arthritis and rheumatoid conditions, London, 1929, 113.
SCHIERBECK, quoted by REID, E. W. (Schäfer), 671, "Textbook of Physiology," 1898.
SILVERS, S., FORSTER, W., and TALBERT, G. A., *Amer. Journ. Physiol.*, 1928, lxxxiv, 577.
TALBERT, G. A., *ibid.*, 1919, l, 433; *ibid.*, 1922, lxi, 492.
TALBERT, G. A., FINKLE, J. R., and KATSUKI, S. S., *ibid.*, 1927, lxxxii, 153.
TALBERT, G. A., and HAUGEN, C. O., *ibid.*, 1927, lxxxi, 74.
USHER, B., and RABINOVITCH, I. M., *Arch. Derm. and Syph.*, 1927, xvi, 706.
VASS, C. C. N. Personal communication.
VASS, C. C. N., and MCSWINEY, B. A., *Journ. Soc. Dyers and Colourists*, 1930, 190.

Section of Therapeutics and Pharmacology

President—J. H. BURN, M.D.

[*February* 13, 1934]

Therapeutics with Hormones of the Ovary [1]

By Dr. C. KAUFMANN (Berlin)

ABSTRACT.—The proliferation of the endometrium in the first half of the normal cycle is caused by the follicular hormone. The transformation into the secretion phase in the second half is caused by the hormone developed by the yellow substance of the corpus luteum. The term "menstrual" bleeding must be preserved for the discharged endometrium which has been proliferated first by the follicular hormone, and then transformed into the secretion phase (pregravid phase) by the corpus luteum hormone. The growth of the uterus in childhood and its pubescence depends on the follicular hormone (vegetative activity of the ovary), just as does the preservation of turgor in the genitals of the puberal woman. Many years ago, cyclic genital activity in the castrated animal was first produced by the injection of hormone, and this effect is now employed as a test for ovarian hormones. I succeeded eighteen months ago in producing complete menstruation in the castrated woman. The size of the doses of ovarian hormones administered is the important factor. In numerous experiments I have shown that—according to our present conceptions—very large doses of follicular hormones are required to produce the proliferation phase of the endometrium. The required dose is about 200,000 mouse units (= 1 million international units). For transformation of the proliferated endometrium into the secretion phase, 35 rabbit units of corpus luteum hormone are needed. The doses of follicular hormones up to now employed in therapeutics do not exert any traceable influence on the endometrium of the castrated woman. Neither have I noticed, that with doses of 600 or 1,000 mouse units, a shrivelling of the uterus which is due to long lasting functional troubles may be done away with. I have therefore proceeded to treat serious hormonal affections of the ovaries with very large doses of ovarian hormones.

This paper reports on: (*a*) The effect of the follicular hormone on the hypoplastic uterus, in primary and secondary amenorrhœa; (*b*) spontaneous regulation of the cycle in secondary amenorrhœa also after treatment; (*c*) the treatment of symptoms produced by castration and at the climacteric; (*d*) the treatment of genital bleeding with corpus luteum hormone.

ZUSAMMENFASSUNG.—Die Proliferation der Uterus schleimhaut (Endometrium) in der ersten Hälfte des normalen Cyklus ist Folge der Follikelhormonwirkung. Die in der 2.Hälfte des Cyklus stattfindende Umwandlung in die Sekretionsphase erfolgt unter Einfluss des vom

[1] I am indebted to Dr. Loretz for the translation of this paper.

Gelbkörper gebildeten Corpus luteum Hormons. Der Begriff die "menstruelle" Blutung muss vorbehalten bleiben für die mit Blutung erfolgende Abstossung einer durch Follikelhormon proliferierten, dann durch Corpus luteum Hormon in die Sekretionsphase (praegravide Phase) umgewandelten Uterusschleimhaut. Wachstum des Uterus in Kindesalter und Pubertät ist ebenso wie die Erhaltung des Turgors im Genitale der geschlechtsreifen Frau Folge ständiger Follikelhormonproduktion (vegetative Eierstocksfunktion). Während im Tierexperiment die Reproduktion der cyklischen Genitalvorgänge durch Hormonzufuhr beim kastrierten Tier bereits vor vielen Jahren gelungen ist und als Testverfahren für die Ovarialhormone benutz wird, ist bei der kastrierten Frau dieses für die Dosierung der Ovarialhormone wichtige Experiment mir vor 1½ Jahren gelungen. In zahlreichen Versuchen weise ich nach, dass zum Aufbau der Proliferationsphase des Endometriums für unsere bisherigen Begriffe ungeahnt grosse Dosen Follikelhormon notwendigsind. Die Dosis beträgt etwa 200,000 Mäuse-Einheiten = 1 million internationale Einheiten. Zur Umwandlung der proliferierten Schleimhaut in die Sekretionsphase sind 35 Kaninchen-Einheiten Corpus luteum Hormon notwendig. Die bisher in der Therapie verwendeten Follikelhormondosen üben auf die Uterusschleimhaut kastrierter Frauen keine nachweisbare Wirkung aus. Ebensowenig habe ich bei der bisher üblichen Therapie mit täglich 600 oder 1000 M.E. Follikelhormon ein Wachstum des bei längerdauernden Funktionsstörungen so häufig geschrumpften Uterus gesehen. Auf Grund der oben angedeuteten Versuche bin ich dazu übergegangen, schwerere Hormonstörungen der Ovarien mit hohen Dosen der Ovarialhormone zu behandeln.

Ich werde berichten: (*a*) über die Wachstumswirkung des Follikelhormons auf den hypoplastischen Uterus bei primärer und sekundärer Amenorrhoe; (*b*) über die Spontanregulierung des Cyklus bei sekundären Amenorrhoen auch nach Aufhören der Behandlung; (*c*) über die Behandlung schwerer Ausfallserscheinungen nach Kastration und im Klimakterium; (*d*) über die Behandlung genitaler Blutungen mit Corpus luteum Hormon.

RÉSUMÉ.—La prolifération de l'endomètre pendant la première moitié du cycle normal est due à l'hormone folliculaire. La transformation en phase sécrétoire pendant la seconde moitié est due à l'hormone de la substance jaune du corps jaune. Le terme hémorragie "menstruelle" doit être réservé pour l'expulsion de l'endomètre, proliféré d'abord par l'hormone folliculaire, puis transformé en phase sécrétoire (phase pré-gravide) par l'hormone du corps jaune. La croissance de l'utérus pendant l'enfance et la puberté dépend, ainsi que la préservation de la turgor des organes génitaux de la femme, de l'hormone folliculaire (activité végétative de l'ovaire). Il y a déjà bien des années que l'activité génitale cyclique de l'animal castré a été reproduite au moyen d'injections d'hormones, et cet effet est employé aujourd' hui comme épreuve pour les hormones ovariennes. J'ai réussi il y a un an et demi à produire la menstruation complète chez la femme castrée. Le facteur important est le dosage des hormones ovariennes. J'ai montré par beaucoup d'expériences qu'il faut de très hautes doses d'hormone folliculaire, selon nos idées actuelles, pour produire la prolifération be l'endomètre. La dose nécessaire est de 200,000 unités de souris (= 1,000,000 d'unités internationales). Pour produire la phase sécrétoire de l'endomètre proliféré il faut 35 unités de lapin d'hormone du corps jaune. Les doses d'hormone folliculaire employées en thérapeutique jusqu'à présent n'exercent aucun effet appréciable sur l'endomètre de la femme castrée. Je n'ai pas observé non plus qu'avec les doses de 600 ou 1,000 unités de souris par jour employées jusqu'à présent on puisse influencer le rétrécissement de l'utérus qu résulte des troubles fonctionnels de longue durée. J'ai donc traité des affections graves de l'ovaire par de hautes doses d'hormones ovariennes.

Je parlerai: (*a*) De l'effet de l'hormone folliculaire sur l'utérus hypoplastique dans l'aménorrhée primaire et secondaire. (*b*) De la régulation spontanée du cycle menstruel après le traitement dans l'aménorrhée secondaire. (*c*) Du traitement des symptômes dus à la castration et à la ménopause. (*d*) Du traitement des hémorragies génitales par l'hormone du corps jaune.

THE theme allotted to me is the therapeutic measures emerging from our present knowledge of ovarian hormones, and I may safely assume that the most important information gained from animal experiments is already known to you. If we wish to form a clear conception of the effect of the ovarian hormones on the genitalia,

particularly the uterus, of a sexually mature woman, it is most convenient to take the normal monthly menstrual cycle as a basis.

We will take as an example a woman who menstruates at regular intervals of twenty-eight days between the first day of one period and the first day of the next. What are the changes which take place in the uterus and ovaries during this time? In the endometrium, we differentiate between the basal and the functional layers of the mucous membrane, in accordance with the views of R. Schröder. The lowest layer of the mucous membrane, the so-called basal layer, does not take part in the monthly cyclical changes. It serves solely as a source for the regeneration of the mucous membrane after it has been destroyed during menstruation. The layer of mucous membrane which is developed from the basal layer, and which undergoes the cyclical changes which we are about to describe, is called the functional layer. In the first ten days after menstruation the mucous membrane grows considerably

FIG. 1.

this phase is known as the proliferation phase. This growth and modification of the endometrium is due to the influence of the ripening graafian follicle. In the second half of the cycle the proliferated mucous membrane is converted into the secretory phase. This latter change is brought about by the influence of the corpus luteum, which is developed from the ripe follicle. When the corpus luteum retrogresses, menstruation commences. At the time of menstruation the mucous membrane which is in the secretory phase is thrown off together with hæmorrhage.

The details of the changes in the endometrium are shown in the accompanying illustrations of three microscopical sections.

Figure 1 shows the narrow layer of mucous membrane, shortly after menstruation. Here only basal mucous membrane is present.

Figure 2 shows the increase in breadth of the mucous membrane at the end of the first ten days of the cycle.

This stage of development—the proliferation phase—is coincident with the growth of the graafian follicle in the ovary. To-day we know with certainty that the follicle produces this endometrial growth by means of the œstrin which it elaborates.

In the second half of the cycle the follicle, after the escape of the ovum, is converted into a yellow body or corpus luteum, which produces a second hormone, totally different from œstrin biologically, but closely related to it chemically. The

FIG. 2.

corpus luteum hormone transforms the proliferated mucous membrane into the secretory phase.

This change is shown in figure 3. The marked convolution of the glands is a feature of the secretory phase.

The whole purpose of these changes is to produce ideal conditions for the nidation of a fertilized ovum. If the ovum does not become fertilized, this endometrial development is no longer of any value. The corpus luteum retrogresses unless the presence of the fertilized ovum stimulates it to persist. The retrogression of the corpus luteum, and the consequent withdrawal of its hormone, lead to menstrual bleeding, that is to say, the highly developed mucous membrane is destroyed by hæmorrhage and is rejected together with the extravasated blood. It is most important

to impress this clearly defined conception of menstrual bleeding upon our minds. In true menstrual bleeding in a healthy woman, the endometrium which has been brought to the proliferation stage by the action of œstrin, and subsequently transformed into the secretory phase under the influence of the corpus luteum hormone, is rejected, accompanied by hæmorrhage, as a result of the cessation of the action of the corpus luteum hormone. This important point has been constantly emphasized in England, by Shaw. Particles of the discarded mucous membrane can be histologically demonstrated in the menstrual discharge. Thus, when attempting to reproduce menstruation experimentally by the administration of hormones, only those hæmorrhages should be regarded as true menstrual bleeding in which morsels

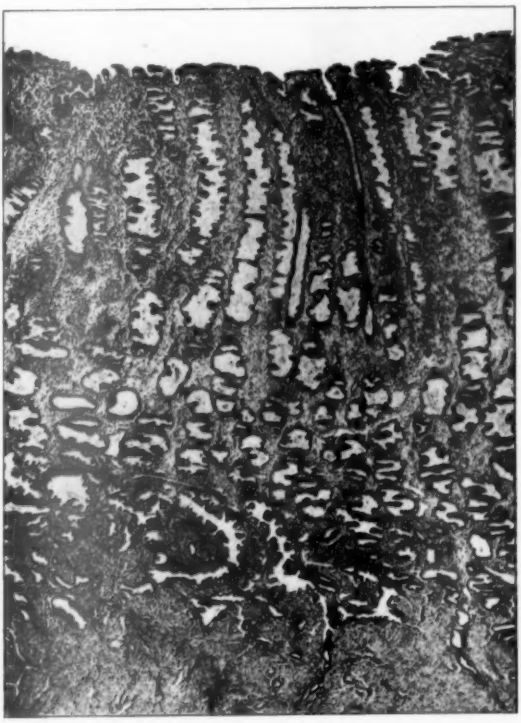


FIG. 3.

of mucous membrane, showing the changes typical of the secretory phase, can be demonstrated histologically. In the life of the sexually mature woman this train of events is repeated at regular intervals from the beginning of the first menstrual period until the onset of the menopause, unless it be temporarily suspended by the nidation of a fertilized ovum and the resulting pregnancy.

Even before the occurrence of the first menstrual period, during so-called puberty, the ovary exercises a hormonal function, in that numerous immature follicles secrete œstrin. The effect of this activity is to produce the proper growth of the uterus and to control the turgidity of the entire genital apparatus, including the vagina. The

whole follicular apparatus continues to produce œstrin even in the sexually mature woman and thereby maintains the uterus in the normal condition of turgidity. We shall see later that individuals exist in whom this so-called vegetative function of the follicles is deficient. In these women, as a result of the lack of œstrin, the whole genital apparatus remains in the condition typical for the young girl before the onset of puberty. It must be remembered that this vegetative function of the follicular apparatus comes into play years before the appearance of the first menstrual period and still continues after the commencement of the menses. With this fact before our minds, it will be at once obvious how difficult and prolonged treatment must be in women in whom this function of the ovaries is deficient.

The knowledge that the above described changes in the ovaries and uterus take place during the monthly cycle, in the sequence shown in our figures, was obtained in anatomical experiments. These are associated with the names of Hitschmann and Adler, Robert Meyer and Robert Schröder. Animal experiments have proved that œstrin produces the proliferation of the endometrium, and that the secretory phase is brought about by the subsequent action of the corpus luteum hormone. The brilliant results obtained in experiments on castrated monkeys showed that these cyclical changes in the uterus could be accurately imitated by the administration of the two hormones. With this knowledge it was natural that many observers attempted to reproduce the menstrual cycle in castrated women by the same means. Nevertheless, these attempts were unsuccessful. Various authors described changes in the endometrium resulting from the administration of hormones to castrated women, but none of the descriptions will bear close criticism.

After many vain attempts I constantly occupied myself with the following question: Why is it that we can reproduce the sexual cycle so accurately in animals, whereas in women we have no success? My astonishment at this discrepancy was still further increased by the fact that the American workers, Smith and Engle, were able to produce the complete cycle in a castrated monkey with a menstrual cycle very similar to that of the normal woman.

Two years ago I again took up this question. At this time it was considered useless to administer more than 600 mouse units daily. This contention was based on estimations of the amount of hormone in the urine. In my experience these doses produced no effect whatever on the endometrium of castrated women. At this stage the results of the important and fundamental experiments of Parkes and Zuckermann on the dosage required in female baboons were available. On the basis of these experiments, which unfortunately did not receive sufficient attention from clinicians, Parkes and Zuckermann maintained that the dosage necessary in women must be very much larger than that so far employed.[1] On January 15, 1932, speaking at a meeting of the Section of Obstetrics and Gynæcology of this Society, Parkes prophesied with remarkable foresight that the dosage necessary in women would be in the neighbourhood of 500,000 mouse units. I was fortunate enough at this time to witness the experiments of Schoeller, Dohrn and Hohlweg, on the dose necessary for the female baboon, which they were then carrying out in order to confirm Parkes's work. Impressed by these, I immediately decided to work with much higher doses.

Even with much higher doses the results were at first unsatisfactory. Only when I employed a dose of 1,000,000 international units of œstrin—a truly colossal figure in comparison to our previous estimates—was I successful. With this amount I was able to produce changes in the endometrium of a castrated patient in every way comparable to the normal physiological condition in the healthy woman. We see, therefore, that the whole problem is a question of dosage.

In the following figures you will see the results of my first experiments.

[1] *Proceedings*, 1932, xxv, 569 (Sect. Obst., 23).

My patient was a 21-year-old girl who had been castrated five years previously on account of dermoid cysts in both ovaries. Before the commencement of hormone therapy the uterus was in an atrophic condition, only isolated simple tubular glands being present in the shrunken stroma.

Figure 4 shows the condition of the endometrium of the same patient after the administration of 1,000,000 international units of œstrin and 35 rabbit units of corpus luteum hormone. The mucous membrane has grown enormously and is in the secretory phase. Its condition corresponds exactly with that found in the normally menstruating woman a day or so before the commencement of the period. In this first experiment I did not wait for the occurrence of menstrual bleeding but removed the portion of endometrium which you have just seen as soon as the hormone administration was complete. I felt convinced that this highly developed mucous membrane would be subsequently discarded, accompanied by hæmorrhage. However, in order to be absolutely certain, I repeated the experiment and this time I waited for the onset of menstruation. Bleeding commenced two days after the

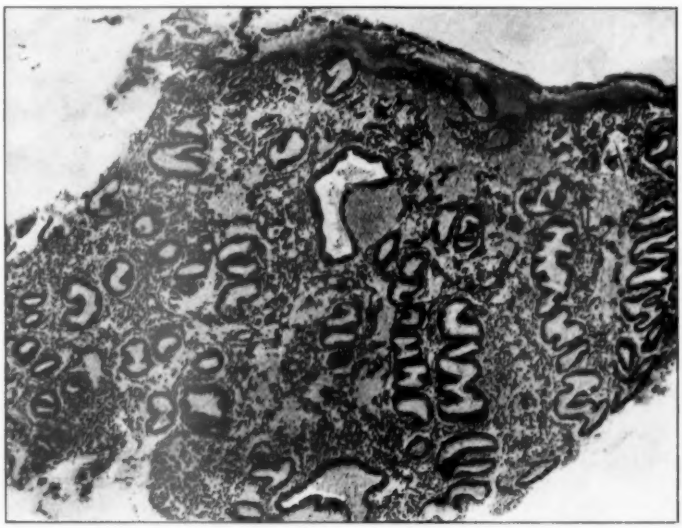


FIG. 4.

last injection of corpus luteum hormone. In the discharge were particles of mucous membrane, which histologically presented the appearance shown in the next figure.

Figure 5 (p. 48) shows a section of endometrium with markedly convoluted, actively secreting glands. Abundance of glycogen was demonstrated in the glandular epithelium and showed that the glands are in a condition of marked functional activity. According to the investigations of Aschheim, Driesen and Wegelin, this histological picture is characteristic of an actively functioning endometrium.

I was thus able for the first time to reproduce exactly the normal cycle in a castrated woman. At the same time this experiment showed that the two ovarian hormones, œstrin and corpus luteum hormone, are the only hormones required to produce the full functional development of the endometrium.

As the dosage question seemed to me to be of the greatest importance, I dedicated

my next experiments to the solution of this problem. There is no point in recapitulating the details of these experiments here. Suffice it to say that in order to bring about the normal degree of proliferation, the most suitable dose was found to be 1,000,000 international units of œstrin. Growth of the mucous membrane can be obtained with smaller doses but these do not produce the same degree of development as is found in the healthy woman at the end of the proliferation phase. I particularly wish to emphasize this point because other observers have frequently maintained that the proliferation phase may be produced with smaller doses.

When photographs of mucous membrane are published as proof of the hormonal action on the endometrium, we can with justice demand that a positive hormone effect can only be claimed when the mucous membrane shows a certain degree of resemblance to the condition of the endometrium which we know to be typical of the normal cycle. Unfortunately several papers which have recently been published do not appear to me to satisfy this demand.

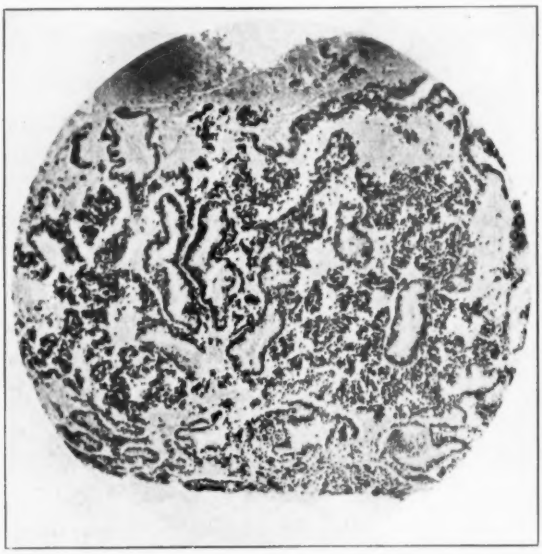


FIG. 5.

To repeat: My experiments showed that to reproduce the proliferation phase in the endometrium of a castrated woman on a single occasion, 1,000,000 international units of œstrin are necessary. Castration necessarily involves the complete abeyance of endogenous hormone production. I carried out my experiments on castrated women because only in this way can we come to a clear-cut decision as to the dosage required for the complete development of the endometrium.

The results above described led me to the conclusion that in the treatment of women who, though not castrated, are suffering from severe ovarian disturbances, the low doses of hormone previously employed must be useless.

Before we turn to the results of treatment in sick women we must first answer the following question, "What happens if we administer too much œstrin?" Experiments to this end were also carried out on castrated women.

We gynæcologists frequently encounter the well-known clinical syndrome of cystic hyperplasia of the endometrium accompanied by totally irregular and often very severe hæmorrhage. Even before the era of hormones, anatomical investigations had enabled us to form a correct conception of the evolution of this malady.

In glandular cystic hyperplasia the normal cycle of development, of which regular menstruation is the outward sign, is completely disturbed. At the end of the normal proliferation phase, that is, some fourteen days after the previous period, the mucous membrane continues to grow and becomes much higher than in the normal condition. In addition, the glands are cystic and dilated. After some time hæmorrhage, which is frequently of a severe nature, takes place from this over-proliferated mucous membrane.

The question immediately arises: "What endocrine process underlies this condition of the endometrium?" You will remember that in the middle of the normal menstrual cycle the mature graafian follicle bursts and that after the expulsion of the ovum it is transformed into a corpus luteum.

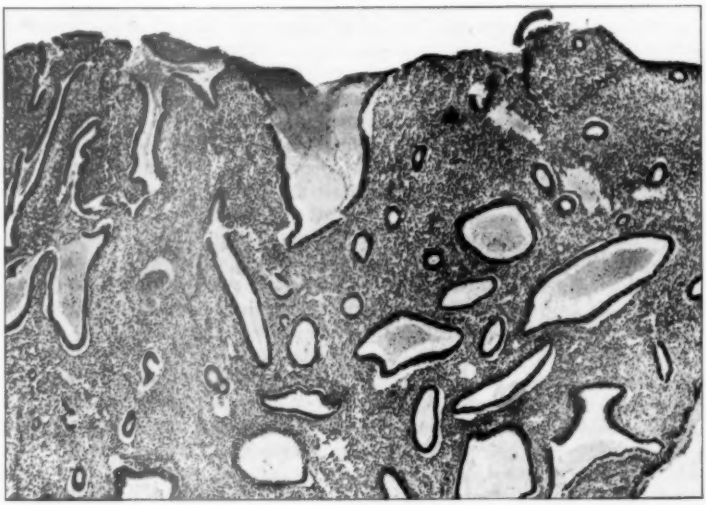


FIG. 6.

In cystic hyperplasia the follicle does not rupture and no corpus luteum is formed. The enlarged persistent follicle continues to produce œstrin and excessive proliferation of a pathological nature is the result. In this way cystic hyperplasia of the endometrium is brought about.

If the above explanation is correct it should be possible to produce true cystic hyperplasia of the endometrium in a castrated woman by administering excessive doses of œstrin. I also succeeded in this attempt, although very large doses were necessary; I was obliged to administer over 5,000,000 international units of œstrin, spread over several weeks, in order to obtain the true picture of cystic hyperplasia.

The result of the experiment is seen in the above illustration, fig. 6, which shows numerous dilated cystic glands. None of these glands, however, is convoluted and none contains glycogen. The characteristic signs of the corpus luteum hormone

function are therefore absent. The result of this experiment explains the ætiology of this common gynæcological disorder.

We see, therefore, that too small a dose produces insufficient proliferation, whereas too large a dose produces cystic hyperplasia of the endometrium.

It is unfortunate that we have to express ourselves in such enormous figures and I would like to make a few observations on this point. I myself was at first greatly perturbed at the thought of having to work with hundreds of thousands of mouse units. For several years we had been under the erroneous impression that it was possible to produce proliferation of the endometrium in a woman with a few hundred rat or mouse units. We now know that this is impossible and we also know the dose necessary in a castrated woman in order to produce full endometrial development. It seems to me desirable that, for the future, we no longer refer to this amount as a high dosage of hormone, but as the physiological dosage. This is all the more reasonable in view of the fact that 50,000 international units correspond to 1 mgm. of di-hydro-œstrin. Thus to produce physiological proliferation we must administer a daily dose of 1 mgm. This effectively disposes of the high figures.

I have discussed this point at length for a definite reason. From the very first I occupied myself with the question as to whether the doses of hormone which I employed were capable of producing any damage. It was found that this was only the case when a gross overdose was administered, as for example in my experimental production of cystic hyperplasia of the endometrium. It may be shown, for example, that harmful effects are produced by administering several hundred mouse units to a mouse. In my opinion it is misleading to draw conclusions relative to human therapy from such observations, since if we are to produce similar pathological effects in human beings, doses of many millions of international units must be used. I mention this point because it is important not to permit erroneous conclusions derived from inadmissible animal experiments to confuse our therapeutic researches.

We may now turn to my therapeutic experiments. All of these were carried out in the Gynæcological Clinic of the Charité in Berlin. My teacher Professor Wagner has given me much help and encouragement throughout these investigations.

The results of the above described experiments pointed the way for my next investigations.

I was now convinced that in amenorrhœa of long standing, and in cases with arrested development of the uterus, small doses of œstrin were useless. I would emphasize here that I rejected all cases with amenorrhœa of short duration, since these do not provide a reliable criterion of the success of treatment. For obvious reasons also, only those cases were selected in which the amenorrhœa was primarily due to deficiency of ovarian hormone.

Before carrying out hormone therapy the patient must be thoroughly examined, in order to exclude the possibility of the endocrine disturbance being secondary to some other disease. Such disturbances are particularly common, for instance, in incipient pulmonary tuberculosis.

Therapeutic experiments on a large scale with high doses of œstrin first became practicable when the technique of injection was simplified by the introduction of highly concentrated preparations. In my first experiments I employed daily injections of œstrin benzoate, 1 c.c. of which contained 50,000 international units. All my later work was carried out with twice-weekly injections of œstrin, 1 c.c. of which contained 250,000 international units. We owe this highly concentrated preparation to the researches of the chemists, Schwenk and Hildebrandt, who showed that hydrogenation converts œstrin into a much more active derivative.

Let us first consider the case of women with primary amenorrhœa accompanied by marked hypoplasia of the genitalia. In most of them the uterus is scarcely larger than a hazel-nut and until recently all forms of therapy have been unsuccessful in these cases. Here the immediate aim of treatment is not to produce menstruation

but to stimulate the infantile uterus to grow. The development of the uterus is dependent upon the presence of the follicular hormone and for this reason I gave such women 500,000 international units of œstrin weekly over a period of months. During the course of treatment no damage or disturbances of any kind was observed. From the first it was obvious that treatment would have to be prolonged, since in these women we have to make up for a hormone deficiency which has persisted throughout puberty, at a time when the uterus of the normal young girl is steadily developing under the constant influence of œstrin.

I have records of five women in whom the uterus, before treatment, was not larger than a hazel-nut. In three of these an astounding degree of growth was obtained as a result of follicular hormone therapy. The length of treatment and the total dosage naturally differed from case to case. In one patient a marked enlargement of the uterus was demonstrable after the administration of 3,000,000 international units.

Another patient's progress was particularly interesting. She was a 19-year-old hospital nurse, fully developed, but with primary amenorrhœa. The body of the uterus was not larger than the tip of the little finger. She came under my care last July. In the first three months she received in all 4,250,000 international units of œstrin. During this period the uterus became softer and more turgid but there was no increase in size. I advised the patient to continue and in the next three months a further 4,500,000 units were administered, so that in the first six months a total dose of 8,750,000 units were injected. In spite of this the uterus still seemed to me to be no larger. For this reason, during the following weeks, I injected 1,000,000 international units weekly. In a short time, the uterus had so greatly increased in size, that, without knowing the patient's history, it would have been impossible to distinguish it from the uterus of a normally menstruating woman. In two of my five cases I had no success. In one of these I was unable to continue treatment for more than six months, and the other showed no improvement after receiving 15,000,000 international units in the space of seven months.

It is worthy of note that in these cases of primary amenorrhœa, only slight hæmorrhages of short duration occurred during this treatment. They must be regarded as due to the influence of œstrin alone, and not as true menstruation. Only on one occasion did a more extensive hæmorrhage occur and in this case histological examination of fragments of mucosa from the discharge showed the typical picture of cystic hyperplasia of the endometrium. After a pause of fourteen days I continued to administer œstrin to this patient and no further marked hæmorrhages were observed.

From the first three cases in this group it will be seen that with sufficient doses of œstrin, even extremely hypoplastic uteri can be brought to an advanced stage of development. We shall have gained very little, however, if the effect of follicular hormone stops here. I think, however, that we are at least justified in hoping that by means of œstrin we may be able to stimulate the whole endocrine system. After all, the only real therapeutic advance will have been made when we are able to produce spontaneous normal menstrual periods in these cases of primary amenorrhœa. Nevertheless, those of you who have experienced the complete failure of every other method of treatment in this condition will understand our satisfaction with our results. It is interesting to note that in our cases, the psychic depression which is so common in these patients, was much relieved by the treatment.

Whereas in patients with undeveloped genitalia a sufficient criterion of the success of treatment is provided by the increase in size of the uterus, in secondary amenorrhœa our only tangible guide is the production of true menstruation. From my experiments on castrated women we may assume that with sufficient doses of œstrin and corpus luteum hormone this must be possible.

I treated my cases of secondary amenorrhœa in several different ways. In one

group I imitated the course of events occurring during the normal menstrual cycle just as I had done in castrated women. These patients, therefore, first received œstrin and afterwards corpus luteum hormone, as is shown in the following scheme (fig. 7).

At first 250,000 international units of œstrin were injected every three days on five occasions. After a pause of three days 35 rabbit units of corpus luteum hormone were given over a period of five consecutive days. On the second day after the last corpus luteum hormone injection menstrual bleeding commenced.

With few exceptions, I succeeded in producing true menstrual bleeding every time in 40 patients. That the hæmorrhage was true menstrual bleeding was proved by histological examination. Indeed, this exact method of investigation is the only reliable method of distinguishing between true menstruation and the so-called "interval bleeding" which takes place from an endometrium in the proliferation phase.

Since, as I stated above, the cases treated were all of an advanced type and of long-standing, I thought it advisable to produce menstruation artificially for three consecutive months.

May 1933

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1 250000 M.E Oestrin	2	3	4 Oestrin	5	6
7	8 Oestrin	9	10	11 Oestrin	12	13
14	15 Oestrin	16	17	18	19 Corpus luteum	20 Corpus luteum
21 Corpus luteum	22 Corpus luteum	23 Corpus luteum	24	25 Menstruation	26 Menstruation	27 Menstruation

Oestrin 250000 M.E. Luteohormon à 7 Rabbit units Menstruation

FIG. 7.

We come now to the important point: What happens when treatment is discontinued? At the present time I can only answer this question in terms of my limited experience and with all due reservation. Completely regular spontaneous menstruation may take place for several months, but in cases of severe disturbance of ovarian function I found that one must be prepared for the reappearance of amenorrhœa after a few months.

Of particular interest was a second group of cases which I treated with œstrin alone, without the aid of corpus luteum hormone.

With doses of 1,000,000 international units, hæmorrhages were observed which were partly "interval hæmorrhages"—that is, bleeding from an endometrium in the proliferation phase—and partly true menstruation—that is, bleeding from an endometrium in the secretory phase. In the latter case one must assume that the ovaries of the patient concerned were able to produce sufficient corpus luteum hormone to complete the work of the artificially supplied œstrin and to convert the endometrium from the proliferation phase to the secretory phase.

As to the permanency of the results thus obtained, I can only say that in the case of two women, treatment with œstrin alone led to the restoration of spontaneous menstruation. This may, of course, have been a coincidence, and we must avoid drawing the conclusion that treatment with œstrin alone is preferable to its combination with the corpus luteum hormone. The number of cases which I have been able to observe is at present far too small to permit of so far-reaching a conclusion.

We may now turn to a somewhat different aspect of my therapeutic experiments, namely, the treatment of exceptionally severe secondary symptoms resulting from castration by operation or irradiation. I am far from recommending the indiscriminate use of high doses of œstrin in all forms of menopausal symptoms, since a large number of these patients may be kept entirely free from their troubles with much smaller doses. Nevertheless, you must all have encountered cases, particularly after castration in young women, in which very severe and hitherto intractable symptoms make their appearance. Frequently recurring "flushings," outbreaks of profuse sweating, almost complete insomnia and the consequent nervous disturbances are characteristics of the condition. Here truly remarkable therapeutic effects may be obtained. In the first two weeks of treatment high doses are advisable, some 500,000 international units being given weekly. After this the dose may be reduced to 100,000 units weekly. All the symptoms usually disappear with astounding rapidity. I would only recommend this treatment if smaller doses prove unavailing, but assuming that the diagnosis is correct, severely ill patients may be completely restored to health and well-being in a very short time.

Lack of time prevents me from discussing the last section of my therapeutic experiments as fully as might seem desirable, but I would like to refer briefly to the treatment of uterine hæmorrhage of ovarian origin. Ovarian dysfunction manifests itself in two ways, amenorrhœa or irregular uterine hæmorrhage. The anatomical basis of the latter is almost always cystic hyperplasia resulting from excessive production of follicular hormone. The application of œstrin is therefore a mistake. On the other hand, a correct and highly effective treatment is to administer corpus luteum hormone. I have treated 50 cases of uterine hæmorrhage of ovarian origin with corpus luteum hormone, with excellent results. For the control of hæmorrhage in the majority of cases quite small doses are sufficient, and in my cases from 5 to 10 rabbit units spread over five days were usually enough. I have occasionally encountered cases in which such doses were insufficient to stop the bleeding, but which yielded to the administration of doses of 60 to 80 rabbit units of corpus luteum as has been described by Clauberg. The great advantage of this form of therapy is that it frequently renders surgical interference unnecessary.

I have now come to the end of my remarks. Doubtless, you are well acquainted with the remarkable results achieved in animal experiments associated in this country with the names of Blair-Bell, Hammond, Marshall, Parkes, and many others, and the no less brilliant chemical researches of Dodds and Marrian. In comparison with the achievements of these workers and those of their scientific colleagues all over the world in the same fields, such as Allen, Aschheim, Butenandt, Corner, Courrier, Doisy, Evans, Laqueur, Loewe, Long, Stockard and Papanicolaou, Zondek—to mention only a few—the clinical results as yet obtained in human therapy appear very insignificant. There is, however, no need for pessimism. With time and patience our results will doubtless improve, and I hope that one day this great army of research workers, from chemists to clinicians, will find in them a sufficient compensation for their sacrifices to the cause of scientific medicine.

Discussion.—Dr. A. S. PARKES said that the recent tendency was to doubt the effectiveness of ovarian hormones, particularly œstrin, in woman, but Dr. Kaufmann had shown conclusively that an exact imitation of the normal uterine cycle could be produced in ovariectomized women by the consecutive administration of œstrin and progestin. Women had thus been brought into line with experimental lower mammals. Further, it had been shown that, while œstrin itself might not have such striking results in woman as it was known

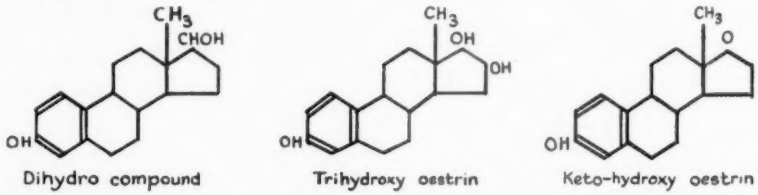
to have in many lower mammals, yet it was clearly the causative factor in the proliferation of the endometrium during the time of follicular growth, and was, moreover, essential for the subsequent action of progestin. The dosage of both œstrin and progestin found necessary by Dr. Kaufmann was actually rather more than would have been expected on a body-weight basis when compared with the amount required for the mouse, rat, and baboon. One million International Units represented 0·1 grm. of pure ketohydroxyœstrin, which was about twice as potent (assayed on mice) as trihydroxyœstrin; 0·2 grm. of the latter would therefore be required. This substance had a maximum solubility in oil of about 5 mgm. per c.c., so that 40 c.c. concentrated oil solution of trihydroxyœstrin would be required to give the necessary dose. This was obviously an inconveniently large amount of oil to give over a short period. For this reason ketohydroxyœstrin should be used where possible.

Professor E. C. DODDS: I, also, am fortunate in having confirmed in detail the results that Dr. Kaufmann has described in his most interesting and brilliant paper.

Dr. Kaufmann very kindly supplied me with particulars of his technique before it was published, so that similar experiments could be conducted over here. Using the same material, we were able to show that menstruation could be produced with the quantities of œstrin and progestin described by Dr. Kaufmann. As in his experiments, our results were checked by curettage and subsequent histological examination.

There is perhaps one point that may not be quite clear to some of the audience this evening, namely, the actual material that was used as the œstrogenic substance. Dr. Parkes has just informed us that the Medical Research Council trials were undertaken with trihydroxyœstrin, and that this substance is considerably less potent than ketohydroxyœstrin, but that it was used for their tests owing to its availability. Dr. Parkes has also pointed out the relatively enormous quantity of trihydroxyœstrin that would be required to produce the same unitage as is demanded by Dr. Kaufmann for his technique.

The material that Dr. Kaufmann used, however, was not the naturally occurring hormone, but was a derivative of ketohydroxyœstrin. It has been shown by Butenandt that trihydroxyœstrin may be converted to ketohydroxyœstrin by distillation in vacuum over potassium bisulphate, and that this materially increased the number of units. Now if the ketohydroxy œstrin molecule be hydrogenated, then the dihydro compound is first formed, and this has four times the potency of ketohydroxyœstrin. Consequently, one quarter the weight only need be given to produce the same effect as ketohydroxyœstrin. By this means Dr. Kaufmann was able to give the enormous doses that he has described in convenient quantities for subcutaneous injection. The relationship between the three compounds is shown graphically as follows:—



Dr. H. GARDINER HILL: I should like to take this opportunity of thanking Dr. Kaufmann and Messrs. Schering for providing me, during the last nine months, with supplies of his concentrated œstrin and corpus luteum extracts. The preparations have been of the same concentration as that which he himself uses—œstrin, 50,000 mouse units per dose, proluton 10 rabbit units per dose. The method of administration has been as directed by Dr. Kaufmann, that is, doses of œstrin have been given on the 1st, 4th, 8th, 11th and 15th of the month, whilst the proluton has been given subsequently on five consecutive days, the 19th, 20th, 21st, 22nd and 23rd. The injections have been made intramuscularly, and only in one case has there been any local reaction.

I will now give briefly the results of my experience with these extracts, and I think it will be agreed that they confirm, as far as they go, Dr. Kaufmann's own observations. I can give details of six cases, in which the extracts have been given a trial. The first two were straightforward cases of secondary amenorrhoea in otherwise normal married women, aged 25 and 33 respectively. The secondary amenorrhoea had been of two years' and seven years'

duration respectively. Both were sterile. Both had been examined by a gynæcologist, and no pelvic abnormality was found, except that in the second case there was a slightly atrophied condition of the cervix and uterus. Both were normal from the point of view of secondary sex characters. In the first, menstruation (since puberty at the age of 15) had been quite regular, up to the onset of the amenorrhœa. In the second, menstruation began at the age of 11, was somewhat irregular until marriage, and subsequently normal until the period of amenorrhœa started. In the first case amenorrhœa dated from a shock, in the second case it followed a miscarriage. Both had received numerous courses of treatment with various ovarian extracts, but in neither had any effect been observed.

The first patient (secondary amenorrhœa two years) began her first course of œstrin-proluton in May 1933. The last injection of proluton was given on May 25. Forty-eight hours later, a hæmorrhage occurred and lasted four days. This, according to the patient, seemed to be in every way like a normal period. No further treatment was given until August. In June and July no period came on. On August 2 the second course was begun, finishing on August 24. Hæmorrhage occurred on August 26, i.e. two days after the last injection—and lasted four days. No further treatment was given until November, and the periods in September and October were missed. The third course in November resulted in another loss for four days, two days after the last injection of proluton.

In the case of the second patient (secondary amenorrhœa, seven years), the first course was begun in July and finished on July 27. A hæmorrhage occurred fifty-six hours after the last injection of proluton, and lasted four days. No further treatment was given until November, and no periods occurred in the interval. The final injection of proluton in the second course was given on December 24 and a hæmorrhage occurred twenty-six hours later. In this case the losses lasted again for four days and the patient herself considered that they corresponded in every way to those of a normal period. I heard from her a day or two ago to the effect that no period had come on in January.

The next two cases were of a slightly different type, in women aged 24 and 23 respectively, with secondary amenorrhœa of six years' and fourteen months' duration respectively. In the first case puberty had occurred at the age of 15, and menstruation had always been regular until the period of amenorrhœa began. In the second case puberty began at the age of 12, and menstruation had always been regular until the period of amenorrhoea. Both these individuals were quite normally developed from the point of view of secondary sex characteristics. Clinically, they should, I think, be regarded as typical cases of anorexia nervosa. In both instances, the onset of the period of amenorrhœa coincided with a nervous breakdown. In both the chief symptom was a very striking loss of appetite, with loss of weight. The first patient lost 3 st. and the second lost 3½ st. in weight. This particular type of amenorrhoea is generally the most resistant to any form of ovarian therapy. The first patient was treated with œstrin-proluton in December, and the last injection of proluton was given on January 10. A hæmorrhage occurred forty hours later, and lasted for five days. Sufficient time has not elapsed for me to be able to give any information about the subsequent period. In the second case, the last injection of proluton was given on January 30, and a hæmorrhage occurred forty-eight hours later. Sufficient time has not elapsed in the case of this patient also to furnish information about any subsequent period.

The remaining two cases are of a very different type, both examples of primary amenorrhœa in infantile individuals. The first patient, aged 19, had never menstruated, and there was no development of the secondary sex characters. The general condition rather suggested a mild grade of eunuchoidism. There was no evidence of any pituitary lesion. Two courses of œstrin-proluton were given, but without any effect. The second case in this group was also an instance of primary amenorrhœa and infantilism. The clinical condition of this patient suggested an anterior lobe pituitary deficiency. The girl was short and somewhat disproportioned, and there were no secondary sex characters. This individual was given a course of œstrin-proluton without any effect either on menstruation or the secondary sex characters.

To sum up, therefore, my experiencies with Professor Kaufmann's extracts, it would seem that in secondary amenorrhœa, even the most resistant cases respond to this treatment, that is, a hæmorrhage has resulted, usually within two days of the last injection of proluton, in every case treated. On the other hand, there is no instance in this series of a subsequent hæmorrhage occurring spontaneously. In neither of the married women was there any beneficial effect with regard to sterility. In the two cases of primary amenorrhœa and infantilism treated, there has been no striking change.

The Failure of Œstrin as a Means of Inducing Labour.

By Aleck Bourne, F.R.C.S.

Experimental work on small laboratory animals would lead us to expect that large doses of œstrin injected towards the end of pregnancy would induce labour, either by direct stimulation of the uterine muscle, or by rendering it sensitive to other oxytocic (Parkes and Bellerby) influences already present in the body. There is still some confusion on the effect of œstrin on the uterus even in small animals. Some workers maintain that it does definitely sensitize the uterine muscle to the action of pituitary extract, while others state that this apparent sensitization is due to a contaminating body in the œstrin used. Experiments carried out on guinea-pig uterine muscle *in vitro* show that pure œstrin has either no sensitizing effect, or else actually diminishes the reactivity to oxytocin. On the other hand, Robson has shown that when pure œstrin is injected into rabbits, there is a definite increase of the uterine reactivity to oxytocin. Robson concludes a recent paper by suggesting that the increased reactivity of the uterus towards the end of pregnancy depends upon the influences of larger quantities of œstrin circulating in the blood, which reach their maximum at full term and parturition.

The human corpus luteum during the later weeks of pregnancy is a degenerate body, and it is difficult to understand how it can, at this stage, exert any controlling influence on uterine passivity. Further, removal of both ovaries during the second half of pregnancy by no means always produces abortion or premature labour.

Taking all these, and other points, which there is no time to discuss here, into consideration, it would seem that injections of large doses of œstrin during the last four weeks of pregnancy, especially when combined with pituitary extract, should succeed in inducing labour. I have attempted this on five occasions by large doses of œstrin, kindly supplied to me by the Medical Research Council, through Dr. A. S. Parkes.

Case I.—Normal pregnant woman received 4·8 mgm. of trihydroxyœstrin at the thirty-seventh week. No effect. Normal labour at term.

Case II.—A similar case. Normal pregnant woman at thirty-seven weeks was given, 4·8 mgm. of trihydroxyœstrin, with no effect.

Case III.—A woman thirty-eight weeks pregnant received ten doses of 4·8 mgm. over forty-eight hours, with no effect.

Case IV.—A woman thirty-seven weeks pregnant had a dose of 5 units of pitocin on December 6. No effect followed. During the following four days she received 24 mgm. of œstrin, and on December 11 a further dose of pitocin, 5 units. On December 11 and 12, 19·2 mgm. of œstrin, and on December 13 an injection of 5 units of pitocin. No effect of any kind was noted. The total dose employed was 43·2 mgm.

Case V.—A normal woman, pregnant thirty-six weeks, received an initial dose of pituitrin of 5 units. After an hour, when it was obvious that the uterus was insensitive to a moderate dose, she was given twenty injections of 4·8 mgm. over ten days, a total dose of 96 mgm., or nearly 1,000,000 mouse units. After the last dose a final injection of pituitrin 5 units was given, but without effect. Ten days afterwards the membranes ruptured spontaneously and feeble pains began. Cæsarean section was then performed on account of contracted pelvis.

Case VI.—A multiparous woman in labour, in a condition of uterine inertia, was given 4·8 mgm. of œstrin, but there was no obvious effect on the course of labour as judged by the strength of the pains.

The milk supply of this woman was noted by observations on the daily weight of the baby, but here again there was no apparent departure from normal.

It appears from these experiments that œstrin, even in very large doses, does not sensitize the human uterus near to term. It may be that still larger doses may do so, but judging from the complete absence of any reaction in these women, I am doubtful if it will be possible to induce labour by injections of œstrin.

Section of Tropical Diseases and Parasitology

President—H. S. STANNUS, M.D.

[*January* 11, 1934]

DISCUSSION ON SOME ASPECTS OF INTESTINAL DISEASES OF EUROPEAN CHILDREN IN THE TROPICS

Dr. P. H. Manson-Bahr: *Bacillary dysentery.*—Bacillary dysentery is placed first, as it is the most formidable and pernicious visitation in European children in the Tropics, especially in those parts of the British possessions which attract numbers of European settlers. It is important, too, from the point of view of differential diagnosis and treatment. As a general rule, it may be stated that bacillary dysentery in European children runs a more acute and severe course than in those of native races. In small children under the age of 5, the signs of toxic absorption come on more suddenly and are more acute than in adults, and may overshadow the bowel symptoms almost entirely. In these subjects it is the neurotoxic element of the poison which affects the central nervous system. The attack may be ushered in by convulsions, and the child may die in coma before the dysenteric symptoms proper become manifest. There may be an initial pyrexia, or even hyperpyrexia, and the clinical picture, with furred tongue and flushed cheeks, may come to resemble that of typhoid. Most cases of bacillary dysentery in children are caused by the Flexner group of organisms.

As a rule the more evident dysenteric signs and symptoms are not so pronounced as they are in adults. The stools may be diarrhœic more than mucosanguineous, and the particularly distressing tenesmus may be absent.

There is some evidence that Sonne's bacillus plays a great part in the enteritis of children in the tropics. In Japan there occurs a form of infantile enterocolitis known as "ekiri." This is an acute epidemic disease of infants, with sudden onset. cramps in the limbs and collapse. Epidemics are apt to prevail in spring, autumn and summer. Death or recovery may take place within twenty-four hours, and sucklings are never affected. Here again the toxin is especially apt to attack the central nervous system. Adachi (K.), 1921, has isolated Sonne's bacillus from these cases.

Sonne dysentery in children.—Perry (H. M.), 1928, and Bensted (H. T.) found, in cases of enteritis and enterocolitis in children in Egypt, that Sonne's bacillus is mainly responsible. The clinical aspects of the cases were most varied. Buchanan (G.) and Roux (P.), 1930, have also found the organisms responsible for dysentery in

children in South Africa. De Assis (A.) and Mendes (M. O.) have reported the same from Rio de Janeiro.

In all forms of Sonne infection there is a tendency to abrupt onset with pyrexia and a remarkable feature appears to be the association of catarrh of the respiratory tract. Apparently two varieties of Sonne infection can be recognized. [Fraser (A. M.), Kinloch (J. P.) and Smith (J.), 1926.] In one variety the symptoms approximate an acute Flexner dysentery with blood and mucus stools; in the other acute toxic symptoms are manifest and closely resemble those of the Salmonella group, and may rapidly be fatal. [Charles (J. A.) and Warren (J. H.), November 1933.] In the milder types the stools are loose and green in colour, and during this period the abdomen is distended.

Treatment of bacillary dysentery in children merits special consideration, because in essence it presents certain features which differentiate it from bacillary dysentery in adults. Bacillary dysentery in children is relatively a much more toxic disease; convulsions and even coma may be distinctive features. It is, therefore, even more necessary than in adults that bacillary dysentery should be attacked energetically. It is most necessary to combat the toxæmia, and it is generally believed that anti-dysenteric serum does this more effectively than in adults. This serum must be given in sufficient quantities and early in the course of the disease. Bromides and morphia in small doses must be given to control the convulsions and to ease the abdominal pain. The diet must receive attention and milky foods must be withheld, but plenty of fluids in the shape of albumin water or barley water must be administered. Champagne or neat brandy can be given in small quantities. Jellies, ice-cream, milk jellies, egg beaten up in whey should form the main articles of food. Cocaine or morphia suppositories are used to ease the abdominal pain. In dehydrated subjects intravenous or deep subcutaneous injections of normal saline and 5% glucose are indicated.

The saline treatment should be persisted in in appropriate doses. Sodii sulph. 15 gr. should be given three or four times a day till the motions become fæcal in character. A small preliminary dose of castor oil, 1 or 2 drachms, is advisable, as to adults.

The special points in the administration of antiserum are as follows:—

Serum treatment of bacillary dysentery in children.—Though the treatment of bacillary dysentery with antidysenteric serum has now been practised for some thirty years, there appears to be no general unanimity about its utility in all aspects of the disease. But there appears to be general agreement that it is especially efficacious in the toxic form of dysentery as it appears in children, and that it is useful in combating the toxæmia and also in shortening the general course of the disease.

From my personal experience in Fiji, Ceylon and elsewhere, in the treatment of acute bacillary dysentery in children, I have no hesitation in advocating antiserum treatment, and probably the modern sera with their much higher Shiga antigenic power are much more efficacious than those formerly used. It is necessary to emphasize once more that the serum should be administered in sufficient amount and early in the course of the illness. The underlying idea to my mind in giving serum is to prevent, if possible, or to minimize, the coagulation necrosis which is taking place in the intestinal mucosa as the result of the dysentery toxin.

The indications for serum treatment may be based upon the following considerations:—

(*a*) The signs of definite toxic absorption. (*b*) The number of the stools—over twelve in the twenty-four hours, and containing a quantity of blood. (*c*) Rapidly rising pulse-rate and corresponding rise of temperature. (*d*) Cases in which the acute stage with bloody stools, tenesmus and abdominal pain, has persisted longer than three or four days and shows no signs of subsiding.

My personal belief is that the medicinal treatment of bacillary dysentery in children should be preceded by intramuscular injection of from 10 to 20 c.c. of antidysenteric serum. Of course at present this applies to Shiga and Flexner infections, though no doubt in time an anti-Sonne serum will become available also.

Intravenous injection of antidysenteric serum in children is not always possible, or always advisable, so that the intramuscular route presents the most practical channel of introducing the serum quickly, and usually the subcutaneous route is too painful and too slow to obtain the best results.

The intrarectal and the intraperitoneal routes have also been used with favourable results. Lantin (J.), 1921, has used the former method in the Philippine Islands. The serum is introduced through a funnel and a long rubber tube, with the patient in the knee-elbow position; 30 to 80 c.c. of serum can be introduced and retained. Knauer (H.) 1926, favours the intraperitoneal route after four years' experience of the treatment of bacillary dysentery in infants and in children. By this method 100 to 300 c.c. of serum may be given altogether to one patient in repeated daily doses.

The treatment of bacillary dysentery in children by sensitized dysentery vaccines has been extensively employed in Germany in the form of a preparation known as Boehncke's Dysbakta (Schittenhelm and Schelenz, 1918).

Especially in cases in which severe local phenomena are associated with signs of general intoxication, good results are obtained by combining vaccine and serum treatment. Daily doses of vaccine in doses of 0·5, 1·0 and 1·5 c.c. are injected subcutaneously together with a small dose of 10 to 30 c.c. of anti-dysenteric serum which may, if necessary, be repeated.

Amœbiasis in children.—It is more than probable that intestinal amœbiasis may be acquired at any period of life; but it is unquestionably a rare disease in European children, and this is probably due to the general care that is usually exercised in their supervision and in guarding them against sources of infection. I myself have never seen or treated a genuine case of amœbic dysentery in a child under 10 years of age, and it is necessary here to correct a sort of loosely held, but nevertheless widespread belief amongst tropical practitioners, that small European children commonly suffer from this infection and that amœbiasis is apt to occasion epidemics amongst them. It is especially essential that amœbic dysentery should be diagnosed in children with great circumspection and caution, mainly because emetine, that valuable drug which is so indiscriminately and thoughtlessly used, is liable to cause the gravest toxic manifestations in young people. Personally I believe that the rarity of amœbic dysentery in children lies in the nature of the dietary which is usually dispensed to European children in the tropics, and also the uncertain but certainly very prolonged incubation period of the disease. They are really very few authentic records of amœbiasis in European children.

My own case was in a boy aged 10 years and 10 months, who had one attack of what appeared to be dysentery, in Shantung, China, when he was 9 years old. Returning to England in March 1927, he had one apparent attack of dysentery in December of that year, and was seen by me on his third relapse in February 1928. He was then passing four typical blood-and-mucus stools daily. His fæces contained numerous active *Entamœba histolytica*, and he reacted well to combined emetine, bismuth iodide, and yatren treatment.

Perry (H. M.) and Bensted (H. J.), 1926, have shown in Cairo that amœbiasis in infants is comparatively common amongst the poorest inhabitants, especially when they have been weaned from their mothers, and according to their tables *E. histolytica* was found in 13·9% of their dysentery cases.

Biggam (A. G.), 1932, described a case of amœbic dysentery in an Egyptian child

in Cairo, aged 3 months. There was also an amœbic abscess of the liver. The child subsequently died of bronchopneumonia, when small amœbic ulcers could be demonstrated in the bowel.

It is to be noted that these figures relate to native children in Egypt, and it is practically the same for India. There, Gharpure (P. V.) and Saldanha (J. L.) (1931) have recently published a table based on an analysis of 426 post-mortem findings in India. Below 10 years of age they found 0·9% of amœbic dysentery and one case of liver abscess. In the decennial period of 11 to 20 on the other hand, the percentage of amœbic dysentery is 12·5 and that of liver abscess 6·1.

I believe, too, that amœbic abscess of the liver is extremely rare in European children. The youngest I have personally observed was a girl aged 16, whom I saw in 1928. A swelling which she first noticed under her right breast turned out to be a liver abscess spreading along the falciform ligament. She had apparently contracted the amœbic infection in Cairo some ten years previously.

My object in stressing the point is to emphasize more than ever the crucial nature of differential diagnosis "in capitals," mainly because it has become the prevailing custom to inject these small patients with emetine immediately dysenteric symptoms become apparent. In genuine amœbiasis in young people I find emetine bismuth iodide and emetine periodide in one grain doses, combined with yatren (quinoxyl) treatment in the customary strength, well tolerated and effective over a period of ten days. But I think that emetine injections are especially toxic to small children. I am constantly having small cachectic and emaciated children brought to me who are obviously suffering from emetine intoxication, the emetine having been given on the mistaken notion that they are suffering from amœbiasis, when the opposite is the case.

I need hardly stress the signs of emetine intoxication—the cachexia, the depressed circulation and the emetine neuritis and myositis.

Young (W. A.) and Tudhope (G. R.), 1926, have ably described the weakness of arms and legs, the muscular wasting and lack of ocular accommodation after emetine therapy. Reed (A. C.), 1931, Rinehart (J. F.) and Anderson (H. H.), 1931, and Epstein (D.), 1932, describe the grave effects of emetine on the cardiac muscles.

There is a form of emetine neuritis to which it is necessary to draw attention; it is a form of progressive muscular atrophy which simulates the scapulo-humeral form and which I have seen on several occasions.

Giardiasis or lambliasis in children.—Giardia intestinalis has the honour of being the first protozoon discovered in man (by Leeuwenhoek in 1681), and is also the flagellate which is extremely common in children, especially European children in the tropics; the rate of infection in these being three times as great as in adults.

Of the intestinal flagellates of man, *Giardia intestinalis* has the strongest claims to be considered pathogenic. It is found in its active state and in the largest numbers when the stools are liquid and diarrhœic, whilst in the chronic stages, when large numbers of cysts are present, the stools may also have distinctive features. In my opinion the symptoms, including the stools of children suffering from chronic giardiasis, resemble those of cœliac disease, and I am glad to find that this receives support from the observations of Reginald Miller in 1926. (*Arch. Dis. in Child.*, 1926, i, 93-98). There is the same persistent diarrhœa, the same enlargement of the abdomen and the same retardation of growth. Treatment of this condition is by no means so satisfactory, and is best carried out by yatren or quinoxyl given by the mouth and by the bowel, by enema.

Cœliac disease.—Cœliac disease is by no means rare in European children from Malaya and India. In the past four years I have recognized at least six instances

of this diarrhœa in my practice. Cœliac disease in tropical children does not differ in any material feature from that so frequently seen in this country. To see it is to recognize it, and to distinguish it from the other forms of gastro-intestinal disease already mentioned. The fat in the stools can be recognized microscopically and, as Bauer has pointed out, the amount appears to be greater than that accounted for by the intake.

It is difficult to escape the conviction that this defective fat assimilation and mal-digestion of carbohydrates, with the abdominal discomfort caused by meteorism and flatulency, has much to do with the excitability and uncontrolled tempers of many European children in the tropics. I recently encountered such an example in a boy, aged 6, from Malaya. The change of temperament and character immediately he had been placed on a suitable dietary, and the more urgent symptoms had subsided, had to be seen to be believed, and were probably more appreciated by his parents than by the small boy himself.

It is not generally realized that cœliac disease in European children may be a sequel to an attack of bacillary dysentery in infancy. In 1931, I saw a boy, $2\frac{3}{4}$ years old, from India, a typical case of cœliac disease consequent upon acute dysentery. The familiar clinical picture of emaciation, typical stools and emaciated abdomen was there, together with defective development of teeth and stunted growth. The customary improvement was noted directly he was placed on a fat-free dietary.

Sprue in children.—Until recently it was the general belief that sprue had never been seen in small children, and in my own experience the youngest child of European origin with undoubted sprue was a boy, aged 13, whom I saw in Ceylon. But on October 27, 1933, at a meeting of the Section for the Study of Disease in Children, Reginald Miller showed an indubitable example of sprue in a boy from Ceylon, aged $11\frac{1}{2}$ years.[1] The diagnosis was readily made upon the history, the characteristic tongue, the megalocytic anæmia, the characteristic stools and the almost miraculous response to a fat-free dietary. Considering the frequency of sprue in adults, especially in Ceylon, where there are some 7,000 Europeans, the occurrence of sprue in children must be extremely rare, and there is a strong conviction that the sprue syndrome is not seen in small infants. I might add that in 1912 and 1913 I travelled over the whole of Ceylon searching for sprue in European children, without success.

Polypus.—It is necessary to refer to this condition, as it not uncommonly occurs in children and may produce many symptoms common to other forms of dysentery. Such a benign pedunculated tumour may produce abdominal pain, tenesmus, and the appearance of blood and mucus in the stools. Such phenomena in a European child in the tropics at once conjure up the spectre of dysentery, and antidysenteric treatment, most usually emetine, is at once applied.

How can one distinguish, on a superficial examination, a case of polypus from other forms of dysentery? The history of recurrent attacks of tenesmus over a prolonged period, without serious interference with the general health, is important. The stools are suggestive, as they are generally formed, and are coated usually with a layer of blood and mucus. From a microscopical point of view the absence of any inflammatory cells and the presence of clumps of red corpuscles are important. The diagnosis is clinched by a sigmoidoscopic examination. The most striking example I have encountered of this condition was in 1931 in a boy, aged 6, from S. Rhodesia, who had been treated for four years for chronic amœbic dysentery. A suspicion of intestinal polypus being aroused, a pedunculated polyp was removed by Mr. T. P. Kilner at 13 cm. up the rectum, with complete ultimate recovery.

1 *Proceedings*, 1933, xxvii, 113 (Sect. Dis. in Child., 1).

Generalized polyposis is another condition sometimes met with in tropical children. This is a terrible affliction, of which I have had several cases. Malignant changes in the polypi almost invariably occur.

Intussusception.—It is necessary to mention intussusception as a differential diagnosis from other forms of dysentery, mainly because it may occur in infants as a complication of acute bacillary dysentery, or it may eventuate as an independent condition altogether, and may be mistaken for acute bacillary dysentery. The stools, for example, may consist almost wholly of blood and mucus and, under the microscope, the cell picture may be very similar.

Colitis in children (forms of colitis other than dysentery).—There is a form of acute idiopathic ulcerative colitis in children under 10 years of age which I have encountered in children from the tropics. It runs an acute course with pyrexia, toxæmia and anæmia, very similar to the disease which we are familiar with in adults. I mention this, not because I am acquainted with anything new regarding its ætiology, but because it is so liable to be confused with other forms of dysentery. Then there is a form of mucous colitis in tropical children, and in my opinion this is almost invariably a sequel to a former attack of bacillary dysentery, and it is aggravated by tropical heat and unsuitable dietary. These children improve immensely on coming to an equable climate and being fed on easily assimilable and palatable European food. I am not in favour of bowel lavage as a form of treatment of this condition in children.

Tuberculous ulceration of the colon, or tuberculous ulceration of the large intestine, is far commoner in children from the tropics, especially in those who have previously suffered from one or other of the forms of dysentery; in fact it is my belief that some of the so-called cases of ulcerative colitis are really of tuberculous origin. But the tubercle bacilli may be very difficult to detect in a blood and mucous stool. The whole stool must be collected, digested in antiformin and continually centrifuged, before tuberculosis can be proved. I have received several surprises in this direction. For instance, a little girl, aged 8½ years, was first seen by me in March 1933; her illness had begun with acute dysenteric symptoms one and a half years previously, and had been considered to be acute amœbic dysentery and received prolonged emetine treatment. Eventually on its being diagnosed as polyposis, exploratory operations were performed. When first seen the child was running a hectic temperature and had four or five blood-stained motions daily. Emaciation and anæmia were extreme, and the child was definitely of a tuberculous type, and there was a small quantity of free ascitic fluid in the abdomen. By washing out the bowel first, by the continuous drip saline method, and then collecting the first blood and mucus passed after the washout, tubercle bacilli were demonstrated in the centrifuged digested deposit. A bad prognosis was given which eventually appeared to have been justified. Up to this time the case had been considered to be the sequel of acute bacillary or amœbic dysentery.

Intestinal disturbances of dietetic origin are extremely frequent in the tropics in European children—probably relatively more so than in children in England. These disturbances are due to unsuitable food, which in the tropics is notably deficient in vitamins. Children who, perforce, have had to be fed "out of a tin," or on tough native meat, chilled or frozen meat, excess of carbohydrates, or native vegetables, present the clinical picture of malnutrition with prominent, flatulent and tympanitic abdomen. It is hardly necessary to point out that these symptoms soon subside on a suitable dietary.

Intestinal helminthic disease in European children.—This too is an important subject and one which calls for more particular attention in tropical children than in those reared in this country.

Tapeworm infection.—Tænia saginata is much the most important, for it is the

commonest and most difficult to dislodge. These can be the most trying cases, and I remember one child, aged 2 years, in Dar-es-Salaam, who contracted the infection by the persistent attempts of the mother to feed it with raw-beef juice! I have no other better suggestion to offer than the time-honoured *Filix mas* with efficient preliminary starvation. I have only encountered one case of *Tænia solium* in a boy aged 5, about ten years ago, and that was dislodged, complete with head, with one dose of 30 minims of carbon tetrachloride followed by a saline aperient.

Ascaris lumbricoides infection is commonly encountered in European children from Hong Kong, Singapore, and Shanghai. It may not occasion any special symptoms, but I have seen it cause a chronic urticaria. There may be associated nervous phenomena. The best treatment is by oil of chenopodium (ascaridole) in capsules of 3 minims each, of which three are sufficient for a child aged 10. This should, of course, be followed by a saline aperient. I have used carbon tetrachloride, 30 minims, also with success, and I consider this treatment better than the time-honoured santonin and calomel.

Ankylostome infection in European children is one that must also be constantly borne in mind. This is the cause of much chronic, but not easily ascertainable, ill-health. I have learned to be suspicious of its presence when the patient is listless and of a sallow complexion. It is a state that easily evades detection unless sought for. I think that the eosinophilia may constitute a useful guide and suggestion for fæces examination. The fæces must always be examined by the Clayton-Lane flotation method, for small infections are the rule and cannot be diagnosed otherwise. The best treatment is oil of chenopodium on one day in the doses already advocated, followed by carbon tetrachloride on the next.

Oxyuris infection is common and extremely difficult to eradicate. The familiar symptoms may be present or not. On one occasion I diagnosed massive oxyuriasis by sigmoidoscopic examination, when I was astounded to see masses of oxyurids wriggling, like miniature eels, along the mucous membrane, towards the lamp of the sigmoidoscope, and over a hundred of these worms were removed.

I am having the best results from treatment by means of carbon tetrachloride (30 minims), followed by an intrarectal injection of quassia 1 : 100; sometimes too, the administration of "butolan" (p. benzyl-phenocarbamin acid ester) 0·25 grm. three times daily, by the mouth, for ten days, is followed by permanently good results, but probably it is more efficacious to combine these methods.

Dr. A. G. Maitland-Jones.—I intend to confine my remarks almost entirely to bacillary dysentery and I wish to emphasize the fact that in my experience it is a relatively rare disease, apart from epidemics of the Sonne type of dysentery, which have occurred in recent years.

At the London Hospital during the last five years only seven cases of dysentery in children have been admitted. The first thing that strikes the observer about these cases is their relative mildness. They all had a certain degree of fever, and blood and mucus appeared in the stools. None of these children was very young; the age was between 2 and 5 years and all of them, within a week or so, appeared to make a complete recovery.

As regards Sonne dysentery, I have had occasion within the last two or three weeks to observe a small epidemic amongst infants, about twenty cases in all, which occurred in a certain hospital. These examples of Sonne dysentery, again, were not seriously ill. Among these twenty cases there were only two deaths—one of which occurred in a case of cœliac disease which had been in hospital for some little time, and the other in a very wasted infant who had been admitted for its advanced malnutrition. The age of the youngest patient was 5 weeks, and eight of the cases

were under the age of 1 year. These patients also all had blood and mucus in the stools.

As regards the diagnosis, I am inclined to say that if a child were ill, with some fever, and blood and mucus in the stools, I would regard the case as one of dysentery, unless I could prove it to the contrary. I personally have never yet seen a case of dysentery which did not have blood and mucus in the stools.

Other conditions causing blood in the stools are polypi and intussusception.

As regards polypus, I do not think there should be much difficulty in distinguishing between that and dysentery; a child with polypus has profuse rectal hæmorrhage, and in between the attacks is perfectly well. Occasionally, of course, there is a certain degree of tenesmus with a polypus.

The differential diagnosis between intussusception and dysentery is a little more difficult. I should stress the importance of vomiting and absence of fever in intussusception, and of course in many cases of intussusception an abdominal tumour can be palpated. Furthermore, in intussusception the attacks of severe colicky pain, between which the infant, at any rate in the early stages, appears to be quite well, should be of aid in distinguishing between intussusception and dysentery.

With regard to treatment, I have little of moment to say. If the diarrhœa should be severe and signs of dehydration be present, I should have no hesitation in giviug the child a continuous intravenous transfusion with Hartmann's solution, to which 10% of glucose had been added. This method of treatment, to combat the anhydræmic intoxication which occurs in severe diarrhœa in the infant, I regard as a distinct advance. I may add that I have had no occasion to use this treatment in any case of this disease under my care.

I would now like to say a few words about the treatment of threadworms in the infant and older child. I hold the view that in many cases much over-treatment of this condition goes on. After all, these worms are not so much a disease in themselves, as a symptom of an unhealthy state of the intestinal tract. I think it is of value in treatment to prevent, if possible, the formation of excessive amounts of mucus in the intestinal tract by giving astringent purgatives such as rhubarb. Rectal injections are, of course, of value; but I have seen many little children whose lives have been made miserable and who have been seriously upset by the almost continual rectal injections to which they have been subjected.

In conclusion, I would like to raise a point which I must admit has no direct bearing on the subject of discussion to-night. I am so often told by parents who live in the tropics that their children must be brought home to England by the time they are 6 or 7 years old, as, otherwise, so I am told, their health suffers. I would like to ask the experts in tropical medicine who are present here to-night if this is so, and, if their health does suffer, to what disease in particular are these children liable?

Colonel F. P. Mackie said that of all the diseases of children in the tropics bacillary dysentery was the most to be feared. Shiga infections were apt to be fulminating, and he had seen institutional epidemics and sporadic cases in private houses where the condition had been mistaken for cholera.

It was important to differentiate Shiga from Flexner infections; the former might be assumed when the onset was sudden, and the course acute, and associated with severe griping, high temperature, and the passing of a large number of stools resembling raw meat scrapings. Flexner infections were not so acute or so sudden in onset; the stools contained less blood and more mucus, and there was less tenesmus and less toxæmia.

The cytology of the stools in bacillary dysentery was characteristic, especially in the Shiga infections, and served to distinguish it at once from the amœbic type, even in the absence of vegetative amœbæ. The dejecta were composed of pus and blood-cells with large macrophages and disintegrated intestinal epithelium.

This enabled a diagnosis to be made by a simple microscopic examination so that early serum treatment could be given, as this afforded the only chance of life in the acutest types of the disease. Shiga infections were quickly followed either by recovery or death, whereas Flexner infections were apt to drag on and become chronic, and in this case children not infrequently passed into a state of inanition and died from exhaustion.

He agreed with Dr. Manson-Bahr that the large majority of dysenteries in children were bacillary, but amœbic infections did occur.

Regarding "lambliasis" (so-called), he was one of those who disbelieved in the pathogenicity of this protozoon. One could see heavy infections in children with normal stools as well as those with liquid stools, and he had seen a sudden influx of these flagellates occur in a case of diarrhœa without causing any access of symptoms and conversely he had seen them as suddenly disappear without altering the clinical course of the disease. He had never seen lamblia or their cysts actually invading the mucosa, though they might be found at the bottom of the crypts of Lieberkühn. This was in contrast to amœbic and balantidium dysentery, in both of which the parasite was a tissue destroyer. During the War he gave up referring to lamblia or any other intestinal flagellate in pathological reports, as he found that the less experienced clinicians were either alarmed at the appearance of this strange creature or else hailed it as a peg on which to hang a diagnosis. Probably the sudden appearance of these parasites was due to some alteration in the intestinal contents or merely to a change in the hydrogen-ion concentration. He thought that the word "lambliasis" should be given up as being a misnomer.

Sir Malcolm Watson said that in his experience few infants in the tropics escaped the syndrome of dysentery. Soon after the eruption of the milk-teeth, inflamed gums, inflamed tonsils and high temperature, were usually found, while blood, mucus and undigested food appeared in the stools. The treatment was simply castor oil, and a reduction in the amount of milk. Any excess of food in an infant or young child, indicated by undigested food, was very frequently associated with blood and mucus in the stool. A single round worm (ascaris) would produce all these symptoms. The cure was the removal of the worm and a reduction in the food. Acute bacillary (Shiga) dysentery was, happily, comparatively rare in European children in Malaya. Before the days of anti-dysenteric serum it caused great anxiety to the physician. It was common among Asiatics. In the Selangor Government Medical Report for the year 1906, he (the speaker) had reported an epidemic which began in the household of H.H. the Sultan, and from there spread to a number of villages. There were 120 cases and 32 deaths. The first cases heard of were reported as cholera, as the disease was virulent, and fatal, in several cases, in four days.

He had seen one case of appendicitis in an infant aged 11 months, in which the signs were blood and mucus in the stools and pyrexia. It was not diagnosed until perforation had occurred, and the operation was too late to save the child. He had also seen a case of intussusception in a European child. The mother reported the child as passing pure blood. Fortunately, the true nature of the case was diagnosed, and operation within four hours of the onset of the symptoms revealed a foot of intussuscepted and deeply congested gut. The operation was entirely successful.

Although these cases with blood, mucus, and pyrexia were so common, he had not lost a case in the twenty-eight years, except the one mentioned ; nor had it been necessary to invalid a child to England on account of dysentery. In this respect his experience was by no means unique. Fletcher reported in his " Dysentery in the Federated Malay States " the result of an inquiry among Government medical officers and private medical practitioners, and among 5,000 Europeans, only two deaths from dysentery had occurred in three years. One was that of a man aged 65, and the other was that of a patient who had suffered much from malaria and was living " as a native, among natives." In contrast, among Asiatics, " during the period 1911-1921, over 47,000 deaths were recorded in a population of about one and a quarter million."

He had not seen sprue in a child, and it was rare among adults in Malaya, as compared with some other countries.

With regard to the age at which children should leave the tropics, he had no hesitation in advising parents in Malaya to keep their children till they were ten years of age. Children did well in that country if they were not treated as hot-house plants, but were made to wear shoes, allowed plenty of freedom and outdoor exercise, and provided they had not suffered much from malaria. With regard to India and the drier parts of the tropics, it depended on the health of the child. These countries were probably more dangerous to children than Malaya, where there was a heavier rainfall.

Dr. Leonard Findlay said that so far as his experience of dysentery was concerned, he was in complete accord with Dr. Manson-Bahr and therefore at variance with his pædiatric colleagues, Drs. Maitland-Jones and Reginald Miller, which was possibly due to the fact that his acquaintance with the disease was mainly as it occurred in the West of Scotland, whereas theirs had been in the South East of England. In the West of Scotland, bacillary dysentery was not uncommon, and occasionally occurred in epidemic form in children's homes, and might attack all the children in a family, but fortunately he had never experienced an outbreak in his own hospital wards. As a rule it was sudden in onset, with fever and the frequent passage of typical dysenteric stools, accompanied by much tenesmus. Indeed so characteristic is the clinical picture that a bacteriological examination of the stools is not necessary, but whenever the stools were examined, at least during the early stage, Flexner's bacillus γ type (which is closely related to Sonne's bacillus) was isolated. He had not found dehydration a marked feature and indeed, in view of the symptoms, there seemed no reason that this should be present. Occasionally, however, just as Dr. Manson-Bahr had remarked, the condition was very acute, with severe nervous symptoms, and death supervened before any true dysenteric symptoms appeared. In his experience this had been most frequent in the unduly well-nourished child of thymo-lymphatic habitus.

In the West of Scotland, bacillary dysentery, although occurring at all ages, was most frequent during the first two years of life, and during this age-period the percentage mortality was also greatest.

Age		Death-rate		No. of cases
Under 1 year	...	65·7 per cent.	...	38
1-2 years	...	23·8 „	...	42
3-5 „	...	22·2 „	...	36
6-13 „	...	9·0 „	...	11

He agreed with Dr. Manson-Bahr that the differential diagnosis from intussusception might cause difficulty, but he could not understand any confusion

arising between it and polypus of the rectum, the characteristic feature of which was simply the passage of a fair amount of blood at long intervals. As complications, he had found bronchopneumonia and pyelonephritis most common, but he had never observed cœliac disease as a sequel. In the treatment of the condition he also believed in the use of dysenteric antiserum, but he had also found of distinct value the daily administration of mag. sulph. in three consecutive doses of 10 to 30 gr. at intervals of one hour until the motions are normal.

Regarding intestinal parasites, the first point he would like to remark upon was their rarity in this country. Ascaris did occasionally occur and give rise to severe symptoms, but as a rule the first evidence of its presence was its appearance in the motion. He was in entire agreement with Dr. Manson-Bahr concerning the difficulty of expelling tænia, and it should always be remembered that there might be more than one worm. In contrast to the general opinion, he considered oxyuris very rare nowadays, and this was true not only of the West of Scotland, but of London as well. If one took the trouble to verify the story of the mother or nurse by microscopic examination of the stools, the presence of these parasites would be very seldom diagnosed.

Mr. H. W. S. Wright said that not the least interesting thing about this discussion was the presentation of diseases common in the experience of anyone working in the tropics, from three or four different angles, e.g. the standpoint of the general practitioner, of the tropical expert abroad, the specialist in tropical diseases, and the pædiatrist working in this country. Perhaps the point of view of a parent and a surgeon would be of some interest. It was amazing, for instance, to hear bacillary dysentery described as a mild disease; in North China, at any rate, it was one of the things every parent had to guard against and fear. The mortality was in the region of 50%. Infection was very apt to occur when children were taken out of their normal, carefully guarded surroundings, and sent, for instance, on a long train journey to the seaside.

Scarlet fever, although not strictly a tropical disease, had, in China, special characteristics, not generally known in this country, which gave it a very high mortality. It was associated with an extremely virulent hæmolytic streptococcus which often caused death from septicæmia within a day or two. Treatment by serum, which frequenntly seemed to lower the temperature and abolish the rash, did not always prevent this septicæmia.

It should be widely known that early blood transfusion from a previously infected adult or child was the best known remedy. It was worth while testing all children for susceptibility and using every known means of passive immunization.

Speaking as a surgeon, it was impossible to emphasize too much the importance of ascaris infections in the production of obscure abdominal conditions. Practically every foreign child was infected at some time or another, many of them nearly all the time. He had many times been asked to see a child with a possible acute appendicitis, in reality suffering from ascaris infection. The child usually had a temperature of about 103°—often higher—and complained of abdominal pain, first generalized and later often referred to the right iliac fossa. The abdomen was a little distended and tender. The differential diagnosis was not difficult if the condition was kept in mind. There was a history of increasing—rather characteristic—irritability in the previous few days, the temperature was higher than was usual in peritonitis, but the pain was more generalized, not so severe, and not accompanied by such marked localized rigidity as in appendicitis.

He had seen intestinal obstruction due to tangled masses of ascaris. The obstruction was of the small intestinal type with a rather gradual onset. This also was often preceded by the toxic irritability and temperature which most parents, both lay and medical, learned to recognize more or less accurately.

Ascaris worms might be the cause of the non-healing of an appendix abscess. He remembered exploring an abscess cavity which would not heal, and finding three dead worms at the bottom.

Section of Epidemiology and State Medicine

President—J. D. ROLLESTON, M.D.

[*February* 23, 1934]

DISCUSSION ON VACCINATION

Dr. S. Monckton Copeman: I hope that what I have to say may serve a useful purpose as a historical introduction to the subject matter of the subsequent papers. To this end I will indicate the various stages in the evolution of administrative and scientific methods in connexion with vaccination, more particularly during the period covered by my official connexion with the Medical Departments of the Local Government Board, and of the Ministry of Health.

In the first place it is perhaps of some historical interest to note that the word "vaccination," which speedily came into universal use, was devised by a Dr. Dunning, of Plymouth Dock, though doubtless based on the terminology of Jenner, who, in his original pamphlet had written of the natural disease cowpox, under the name of "variolæ vaccinæ." This term was doubtless expressive of a pious opinion on the part of Jenner, who, however, never produced any experimental evidence in support of the thesis implicit in this classical and now classic phrase.

Jenner did not originate the suggestion that inoculation of natural cowpox was an efficient preventive of smallpox. Moreover, it would seem that he had been anticipated by Jesty (1774) and others in the attempt at intentional vaccination of the human subject. It may, however, be fairly claimed that he originated the technique of subsequent *variolation* of the patient with the object of demonstrating the production of postvaccinal immunity to smallpox. But, even as regards this latter point, his experiments were so few in number and carried out at such brief intervals of time after the vaccination, as certainly not to justify the assertion that the protection afforded against attack by smallpox was necessarily permanent.

Jenner, however, was possessed of unbounded enthusiasm, in addition to an inquiring mind, and by his persistence at length succeeded in forcing on the notice of the medical profession, and subsequently, of a far wider and more public audience, facts, which, but for his intervention, would probably have remained unregarded as representing merely folk-lore tales of the Gloucestershire dairymaids. And, as has been well said, it is he who compels the world's attention to, and acceptance of, a truth, and enforces or renders possible its application, who confers on mankind that benefit which is the measure of merit.

Vaccination law.—Although, largely as the outcome of an inquiry by the Royal College of Physicians, whose report was submitted to the House of Commons in July 1807, vaccination, according to Simon, gradually became almost universal so far as children of the educated classes were concerned, it was not until the year 1840 that the matter was first dealt with by legislative enactment.

The first Vaccination Act, passed in this year, provided means of vaccination, at the public cost, for the whole population, but left adoption of its advantages entirely optional. It also forbade, under penalty, any attempt to produce smallpox by inoculation.

Thirteen years later, the Act of 1853 made vaccination compulsory, imposing penalties for default on the part of parents or guardians of children.

Dr. Rolleston, in his recent presidential address, laid stress on the interesting fact that, in the preparation of this enactment, the old Epidemiological Society, the parent of our present Section, played a part of no small importance, as was acknowledged at the time by Lord Lyttleton when introducing the Vaccination Extension Bill into the House of Lords on April 12, 1853.

The Act of 1867 repealed all former Acts relating to vaccination, and gave wider powers to Guardians, *inter alia*, allowing payment of expenses incurred by them in carrying the Act into effect. The provision of the 1840 Act, as regards penalizing attempts at production of smallpo xby inoculation, was re-enacted. But evidence of opposition to the provisions of the 1867 Act soon became apparent, and Parliament was petitioned to repeal it. This resulted in the appointment of a Select Committee who presently reported in favour of the protective influence of vaccination against smallpox but declared against multiple penalties for default. Their recommendations were incorporated in the Vaccination Act, 1871. Under this Act, anyone preventing a public vaccinator from taking lymph for subsequent use from any child he had vaccinated, incurred a penalty of 20s.

Royal Commission of 1889.—With the exception of the issue by the Local Government Board of certain explanatory Orders, no further action was taken until 1889, when, in view of increasing opposition to vaccination, and carefully organized resistance to the law, a Royal Commission was appointed, charged with the duty of fully investigating the subject under very wide terms of reference. How thorough the investigation actually was, may be judged from the fact that the Final Report of the Commissioners was not presented until August 1896.

Before this Royal Commission, whose recommendations had, eventually, the effect of totally altering previously existing arrangements in connexion with the operative procedures of vaccination, I was afforded the opportunity of giving evidence, mainly in reference to a method that I had devised—and demonstrated at the London International Hygiene Congress of 1891—for the bacteriological purification and preservation of vaccine lymph by prolonged treatment with a sterile 50% solution of glycerine in water or normal saline. For vaccine freed by this method from "extraneous" micro-organisms I invented the term "glycerinated lymph," which subsequently became official.

The more important recommendations of the majority report included :—

(1) Domiciliary, in place of stational, vaccination.
(2) The use of calf-lymph (the State to provide supply for public vaccinators).
(3) Storage of lymph in tubes, each containing sufficient lymph for the vaccination of one person only.
(4) Antiseptic precautions as regards instruments and treatment of the vaccinated area.
(5) The "conscience" clause.

One of the earliest results of the report of the Commission was the increase of calf-lymph vaccination, to which official recognition was afforded by the Local Government Board who issued instructions to this effect to public vaccinators in February 1897.

For some years previously small quantities of calf-lymph had been issued from the Animal Vaccination Station, in Lambs Conduit Street, which had been founded in 1881 as the outcome of investigations by the late Sir George Buchanan and Dr. Cory. This station was used mainly for the purpose of direct vaccination of children, from calf-to-arm, and of supplying public vaccinators with material with which to initiate periodic stational work in country districts. The original stock of lymph with which the work of this Station was started was a supply of cowpox lymph presented to Sir George Buchanan by Dr. Dubreuhl, of Bordeaux, who, in turn, had obtained it, on November 26, 1881, in the course of an outbreak of cowpox which occurred at a farm in the near-by village of La Fôret.

The Government Lymph Establishment.—Following on the report of the Royal Commission, I received instructions from the Local Government Board to accompany the late Sir Richard Thorne on a tour of the chief vaccination centres in Germany, France and Switzerland. In the course of this work we found that Germany had already adopted the use of glycerinated lymph and domiciliary vaccination, as the outcome of the report of a Commission of which Koch had been President. On our return home we submitted a report to the Local Government Board stating what, as the result of our experiences, appeared to constitute the essential conditions for providing and distributing official supplies of vaccine lymph to meet the necessities of a system of gratuitous domiciliary vaccination.

These suggestions having been accepted by the Government, I was further instructed to make arrangements for the necessary laboratory accommodation, which, in the first instance, was provided by the leasing of a set of rooms at the Lister Institute, the Lambs Conduit Street premises being retained, and after alterations, used for calf-stabling only. The necessary staff was then appointed, the late Dr. Blaxall being placed in charge, with the designation of Chief Bacteriologist.

As the work developed, further accommodation was found to be necessary, and a few years later, H.M. Board of Works erected at The Hyde, Hendon, the magnificent block of laboratories which constitute the present Government Lymph Establishment.

Vaccination Act of 1898.—The Act of 1898 embodied many, though by no means all, of the recommendations of the Royal Commission: (1) It extended the age-period of vaccination to six months after birth; (2) it replaced the system of stational vaccination established under the Act of 1867 by a system of vaccination at the homes of children; (3) vaccination with glycerinated calf-lymph was substituted for arm-to-arm vaccination; and (4) a parent who conscientiously believed that vaccination would be prejudicial to the health of his child might escape penalty for not procuring the child's vaccination by satisfying two justices or a stipendiary or metropolitan police magistrate in petty sessions, of his conscientious belief, and delivering a certificate to that effect to the vaccination officer (Lithiby).

The Act was originally to operate for five years, and it has since been renewed from year to year by the Expiring Laws Continuance Acts.

Relationship of smallpox and vaccinia.—Anti-vaccinists had, for long, been accustomed to stress the absurdity of trying to protect from one disease by the inoculation of another totally different one. Yet, in coining the term "variolæ vaccinæ" Dr. Jenner would seem to have been putting on record his belief that smallpox and cowpox were, in some way or other, definitely related the one to the other. But, as was clearly indicated by Creighton, Jenner "never demonstrated, experimentally or otherwise, that cowpox was biologically akin to smallpox," neither had any other individual, down to the date of Creighton's publication, succeeded in doing so. In other words, to quote from Professor Greenwood's lecture to the Royal Statistical Society—"down to the end of the nineteenth century, vaccination as a prophylactic rested wholly upon an empirical basis."

Some early work of my own on this subject, of which the outcome was reported to the Royal Commission on Vaccination, was not altogether satisfactory. But some years later (*Proceedings* of the Royal Society, 1902, better fortune attended a series of experiments involving the "passage" of variola virus through one or more monkeys, from which, in turn, calves were vaccinated, eventuating in the production of typical vaccinia. These experiments, Professor Greenwood agrees, "were virtually decisive." He points out, moreover, that since my work was published, the technique of biochemistry has been so much further developed that it has been possible to demonstrate the affinity of variola and vaccinia "by methods having the quantitative precision of work in chemical laboratories, which, all of us, whatever

our opinions on the vaccination problem may be, regard as outside the field of rational controversy." Professor Greenwood is here, of course, referring to the work of Mervyn Gordon, Burgess, Craigie and Tulloch.

No longer then is it possible for anti-vaccinators to denounce the folly of trying to protect against one disease by the inoculation of another totally different disease, in view of the very definite proofs, now available, "of that kinship between the cow disease and the disease in man, which Jenner apparently adumbrated but did not prove."

Question of compulsion.—Of recent years a complete change has come over the scene, in consequence of smallpox prevalence all conforming to the exceptionally mild form of the disease now generally known as variola minor, virulent smallpox of the type known to our predecessors having, for many years past, been conspicuous by its absence. The mortality from this mild form of smallpox, which breeds true to type, though with some occasional exacerbation of symptoms, is so small as to be practically negligible. Accordingly it would seem a moot question as to whether it is worth while expending public funds on all the precautionary methods, including isolation in hospital, intensive vaccination of contacts, etc., properly employed in presence of an outbreak of typical smallpox. It has indeed been suggested, with a certain amount of reason, that, except under special circumstances, an outbreak of variola minor should be allowed to "rip." A policy of *laissez faire* under these conditions could hardly conduce to appreciable difference in mortality statistics, yet would, it is further suggested, have the result of protecting the exposed population from any subsequent invasion by ordinary smallpox, without exciting the opposition that insistence on the vaccination of all contacts might arouse. Moreover, it is obvious that substantial economies to the authority would result in the event of non-insistence on the removal of patients to an isolation hospital with their subsequent care and maintenance therein.

In view of the fact that practically all the smallpox which has prevailed of recent years has consisted of this mild variant of the disease, whereas the major type has been almost unknown in this country for the past thirty years, the question as to the desirability of retaining what remains of compulsion in vaccination has obtained more and more prominence of late. Another factor of importance in this connexion which has arisen within recent years has been the recognition of the serious complication of vaccination known as postvaccinal encephalitis. It is true that although the percentage mortality of this complication is high, the total number of cases in proportion to the number of vaccinations performed is very small; while the investigations of the Rolleston Committee have indicated that if certain measures advised by them in their report are generally adopted, this complication—which, it should be added, is not peculiar to vaccination, since it has been known to follow attacks of smallpox, measles and other infectious diseases—is likely to become of negligible importance. Under all the circumstances and especially in view of the fact that it is fully recognized that general vaccination of the community is an impossibility, there would seem nowadays to be a fairly good case for the removal of the compulsory element in vaccination, provided that the necessary administrative machinery be retained in view of possible emergencies.

Virus cultures and lymph supplies.—As the outcome of the great advances in bacteriological science and technique which have come about since the Act of 1898 was passed, and more especially during the past year or two, as regards the cultivation of the specific virus of vaccinia in the fertile egg and other media, it should, before long, become possible to substitute at comparatively small expense, pure cultures thus obtained, for my glycerinated emulsion of calf vaccine pulp, which hitherto has "held the field" in this and other countries since its official introduction more than thirty years ago.

If, and when, it becomes feasible to distribute virus "lymph" prepared in such

manner as may prove most satisfactory, and being, though completely sterile, (i.e. bacteria-free) fully efficient in its action quâ vaccine, I, for one, shall gladly welcome its introduction. If, and when, such a "change over" be considered desirable, it could doubtless be accomplished without having to seek further Parliamentary sanction, in view of the fact that, under Section I (3) of the 1898 Act, the official vaccine lymph with which the public vaccinator "shall offer to vaccinate the child" is defined as glycerinated calf-lymph—or such other lymph as may be issued by the Local Government Board."

Dr. Mervyn Gordon said that the discovery in comparatively recent times that rabbits were susceptible to vaccinia had enabled its serology to be investigated more fully than was previously possible, because it was difficult to house calves and monkeys in ordinary bacteriological laboratories. Three specific antibodies were now known to be evoked by vaccinia virus: (1) a viricidal antibody that inactivated the virus *in vitro*, (2) a complement-fixing antibody, and (3) an antibody that caused visible flocculation of the virus and had recently been shown by Craigie to owe its effect partly to agglutination of the elementary bodies, and partly to precipitation of their soluble contents. Flocculating serum prepared from the rabbit against vaccinia was equally specific for the viruses of variola major or minor and had been shown by Tulloch and Craigie to have a definite practical value in the diagnosis of smallpox. Tulloch and Craigie had also found that such serum had valuable anti-infective properties, and this observation had been said "to raise a hope that smallpox contacts might be passively immunized with a reasonable expectation that the disease would be aborted even in circumstances when vaccination might not prevent infection." With regard to recent work on allergy, Wilson Smith had shown that a boiled extract of vaccinia virus excited a specific reaction in the skin of vaccinated subjects, and Craigie had proved that a similar reaction was evoked by the elementary bodies.

Professor J. C. G. Ledingham.—Five years ago I opened a discussion by this Section on "Vaccination in the light of recent experience."[1] The particular new experiences then offering themselves for consideration were (1) an existing prevalence in this country, on a fairly large scale, of an exclusively mild form of smallpox which apparently showed itself first about 1922, and (2) the recognition of post-vaccinal encephalitis as a possible sequel of vaccination. During the ensuing five years the mild smallpox which had reached its highest incidence of 14,767 cases in 1927 fell rather precipitately to 2,039 in 1932, and in 1933, for which year I have not the official figures, the incidence has probably descended still further. The case-fatality rate has ranged from 1·4 to 4·2 per 1,000—figures very similar to those recorded in the United States, where for 30 years, according to Chapin and Smith (1932), the prevailing smallpox has been of the mild type with an average fatality of 3 per 1,000 and showing no evidence of reversion but very dissimilar, on the other hand, to those registered in, let us say, the Alexandria outbreak of 1932-3 with a mortality rate of 210 or thereabouts per 1,000. In the same period while the incidence of postvaccinal encephalitis had reached double figures in 1923, 1927, 1928, and 1929, only 6, 7 and 2 cases of post-vaccinal nervous disturbance were officially assigned to this category in 1930, 1931, and 1932. It would of course be quite fallacious to imagine anyorderly rise or fall in postvaccinal nervous sequelæ in unison with vaccination figures. What appears to be clear is that incidence of postvaccinal encephalitis has usually coincided in time and place with mass vaccination.

It required some consideration to decide what particular aspects of the problem of vaccination I might profitably devote my remarks to-night as the general

[1] *Proceedings*, 1929, xxii, 507 (Sect. Epid., 9).

situation has changed but little since 1929. I propose to discuss briefly two subjects very relevant to the general problem, viz. (1) the nature of the viruses of smallpox and vaccinia as revealed by quite recent work and (2) postvaccinal encephalitis, a still unsolved mystery, but I should not like to conclude without permitting myself the opportunity of again expressing my personal views on vaccination practice.

The nature of the viruses of vaccinia and smallpox.—In the last five years our knowledge of this subject has advanced materially. It has now, I think, been quite satisfactorily demonstrated by experimental proof that the elementary bodies observed first by Paschen in 1906 in material from smallpox and vaccinia lesions do really constitute the virus elements. By special methods it has been possible to secure these bodies in pure suspension and to show first, that such bodies alone have the power to infect, while the fluid menstruum in which they are suspended is quite inactive (Eagles and Ledingham, 1932), and secondly, that such suspensions can be employed for agglutination tests with the sera of vaccinated animals (Ledingham, 1931). Similarly prepared suspensions of elementary bodies extracted from our mild smallpox cases in England have also been shown to be agglutinable in the presence of sera from smallpox cases (Amies, 1932), and it may be added here that like suspensions of elementary bodies present in the early vesicles of varicella are agglutinated by the sera of chickenpox cases and convalescents (Amies, 1933).

This new knowledge, I need hardly say, possesses diagnostic value, and here I may emphasize a statement made at the Brighton Congress, that the diagnosis of smallpox should no longer be regarded as the peculiar province of certain specially trained clinicians, the laboratory being now in a position to give valuable help in doubtful clinical cases. When the diagnosis lies between variola and varicella the serum of the case will, at the appropriate time, make the diagnosis clear, as there would appear to be no serological relationship between the viruses of variola and varicella.

Nomenclature enthusiasts have already been busy. We now know that quite a large group of viruses possess elements which are just at or slightly below the level of microscopic resolution and I may cite as examples, fowlpox, cowpox, smallpox, molluscum contagiosum, ectromelia, varicella and herpes zoster.

For the pock viruses the genus *Borreliota* has been suggested by Goodpasture (1933), to whose work we owe much, from Borrel, who first observed the elementary bodies of fowlpox in 1904, but time will show whether this somewhat cumbrous generic term will find general acceptance. The virus of variola would be known as *Borreliota variolæ* var. *hominis* and that of vaccinia *Borreliota variolæ* var. *bovis*. The new knowledge must eventually revolutionize much of the technical procedure hitherto current in virus work. It will be necessary, for example, to employ for accurate experiment, only the pure elementary body suspension, now an entirely practical proposition.

Culture of vaccinia.—The culture of this virus has been practised for a hundred years and more on living animals susceptible to the virus, but in the past two years a novel modification of this practice has proved successful in the hands of Goodpasture, Woodruff and Buddingh (1932), who infected the chorio-allantoic membrane of the growing chick embryo.

Nauck and Paschen (1933) in Germany, and Stevenson and Butler (1933) at the Government Lymph Establishment in this country, have also exploited the possibilities of this method of culture which may, for all we know, become the method of election for the mass-production of a bacteria-free lymph. This represents an important advance, the only difficulty that may be anticipated being that of securing at all times of the year a sufficient supply of fertile eggs. It may be asked what guarantee is there that such bacteria-free lymph will retain its potency on

storage. Already there would seem to be quite good evidence that such lymph prepared in the chick embryo retains its potency in the stored state for at any rate months and probably for years. Goodpasture and Buddingh (1933) have during the past fifteen months carried through eighty-five successive generations on the living chick embryo membrane. With lymph of this kind, belonging to the sixth passage and stored at 0° C. for five months, six out of seven persons were successfully vaccinated with typical reactions and one was doubtful. None had shown scars of previous vaccination. Four persons received lymph of the seventy-fifth passage, stored for three months, and all reacted typically. Eight weeks later these successfully vaccinated people were again tested and all gave typical accelerated immune reactions subsiding in seventy-two hours.

The egg method must be reckoned as involving an infection of the living animal but it yields a bacteria-free lymph. There are, however, other methods of cultivating the virus in test-tube media entirely apart from the living animal. I refer to growth in the presence of living or living and growing tissue cells, a method which has also been found applicable to mass production of lymph. The virus has been grown also on media containing no living cells but only their protoplasmic débris (Eagles, 1932, Eagles and McClean, 1931).

For the future, therefore, we may have available in the form of bacteria-free lymph the following types:—

(1) Bacteria-free lymph grown on chick embryo membrane.

(2) Ditto, grown in association with living cells or in media containing no living cells.

(3) Pure suspensions of elementary bodies obtained by high-speed centrifugalization of filtrates of vaccinia.

I may add here that, so far, it has not been possible to show that killed virus possesses any very important prophylactic value, but it is to be hoped that this problem will not be lost sight of. The further exploitation of these bacteria-free lymphs on man is highly desirable and from them we may expect to learn more of the possibilities of the intracutaneous method of inoculation, for which such lymphs would seem eminently suited.

The period throughout which vaccination against smallpox, virus culture and everything connected therewith have been surrounded with a cloak of mystery is fast drawing to a close.

Postvaccinal encephalitis.—It is doubtful if there is any fresh positive information calculated to throw light on the ætiology and mechanism of this rare but serious sequel of vaccination, but the problem must remain in the forefront of interest and the hope of its solution a stimulus to still more intensive investigation of encephalitic syndromes, whether following virus infections or of independent origin. The two reports of the Vaccination Committee published respectively in 1928 and 1930 constitute, it is fair to say, a storehouse of information on this subject from experience gained in this country and abroad up to four years ago. As I have said, the condition has not disappeared from this country, though the annually recorded figures have been very small. Information with regard to this condition in other European countries and in the United States has been available for some time in reports of various national committees, Dutch, German, Swedish, etc., and in reviews submitted to the Office Internationale. In Italy, which only a few years ago was thought to be free from this type of disturbance, there would appear to have occurred, according to Allaria (1932), who reviews the subject, probably about a hundred cases in the previous ten years, but what proportion of these were genuine it is now impossible to say. After the recognition of the existence of postvaccinal encephalitis in England and Holland, other European countries, in which the condition had not hitherto been recognized, appointed commissions which instituted retrospective inquiries, while alleged current cases were submitted to rigorous—and, where

possible, histological—analysis, with a view to excluding other possible causes. Retrospective inquiries must always be more suspect and liable to error, while even current cases of nervous disturbance following vaccination, which occur sporadically and make good recoveries, will always be enrolled with a residuum of doubt in the category of postvaccinal encephalitis. In some series submitted to careful investigation, tuberculous and other forms of meningitis have been quite definitely established as adequate causes of the postvaccinal disturbance and there would appear to be good grounds for the belief that vaccination may cause an exacerbation of concurrent bacterial and other infections, leading possibly to fatal issue. In Germany so much emphasis has been laid on this possibility, that the claim is made that such disturbances would largely disappear if adequate care was taken to select for vaccination only perfectly sound vaccinees harbouring no apparent diatheses. It may be recalled that long before the recognition of postvaccinal encephalitis as a definite entity the warning was given never to vaccinate or to assemble persons for vaccination during outbreaks of poliomyelitis. It is a relief to turn to the solid ground given by histological examination of fatal cases.

Here there has been practically no diversity of opinion, though it must be admitted that certain authorities have felt constrained to ignore the very characteristic histology of typical cases, in their belief that the vaccinia virus is most likely to be the one and only cause. The essential lesion in the central nervous system of fatal encephalitic disturbances following vaccination, smallpox, measles, influenza, and possibly varicella, rubella and mumps, is a demyelination of nerve-fibres in the neighbourhood of blood-vessels, a condition to which Marsden and Hurst (1932) in a recent valuable paper have given the name "acute perivascular myelinoclasis."

These authors, criticizing the view still held by some authorities that the vaccinia virus may be wholly responsible for the condition—since it follows vaccination—emphasize the fact to which others before them have repeatedly drawn attention, that the cerebral manifestations of the virus of vaccinia which occur only when the virus introduced directly into the brain are of an entirely different order, a meningitis only resulting. They would attach even greater importance to the peculiar grouping and massing of such syndromes, both in time and space, in connexion with vaccination, measles and antirabic treatment. It does not appear, however, judging from a recent paper by Getzowa, Stuart and Krikorian (1933) that all cases of nervous disturbance ending fatally in the course of antirabic treatment show the demyelination picture. These authors report the occurrence of two cases of the ascending Landry type, following antirabic treatment, and also a similar case of unknown origin, in which perivascular zones of demyelination were absent, and only widespread involvement of ganglion cells in cord and spinal ganglia was detected.

Marsden and Hurst survey critically the evidence which has accumulated showing that diseases involving lesions of acute perivascular myelinoclasis occur independently—and of late years in increasing numbers, as the communications of Pette in Hamburg, Redlich in Vienna, and Flatau in Poland show. They conclude that though the pathological background may vary considerably in this type of case, to which the names disseminated encephalomyelitis and acute disseminated sclerosis have been applied, yet the histology of certain groups of these cases bears a strong resemblance to that found in the postviral encephalitic complications we are discussing. The one link lacking in the proof that the encephalitis following vaccination or measles is an activated syndrome is the failure, as yet, to show that any virus or pathogenic agent can be recovered from the nervous tissue and communicated to some susceptible animal. Much has been made by critics of the activation theory, of the occasional presence of the virus of vaccinia in the brain or cerebrospinal fluid of fatal cases. While the vaccinia virus has been recovered from the brains of experimental animals after normal vaccination, it has not been

recovered, at least so far, from the cerebrospinal fluid after normal vaccination in man. A German report states that in 75% of eighty-six infants, of 4 to 20 months of age, the virus was demonstrated in the blood on the sixth day, but not after the tenth day. Moreover, it was not detected in the cerebrospinal fluid in fifty-six cases of normal vaccination. On the other hand, there is evidence of its presence in the cerebrospinal fluid in postvaccinal nervous disturbances, which ultimately are found to be due to tuberculosis or some other inflammatory process. Thus Gins (1933) records three cases of this nature: two in which, four weeks and nine days respectively, following normal vaccination, symptoms of meningitis occurred, when the blood and cerebrospinal fluid were found to contain both tubercle bacilli (by guinea-pig inoculation) and vaccinia virus, and a third in which, seven days after vaccination, vomiting occurred, followed on the twenty-first day after vaccination by cerebral symptoms, coma and paralysis. On this twenty-first day vaccinia virus was present and autopsy showed typical tuberculous meningitis. In Gins' opinion if another infection is present, the virus is not normally got rid of. Even when symptoms of encephalomyelitis occur after vaccination, Gins has demonstrated the virus of vaccinia in the cerebrospinal fluid, after the disappearance of these symptoms, and in the case in question there were no residual sequelæ. Hurst and Fairbrother (1931) found that vaccinia did not modify the nervous lesions of poliomyelitis in monkeys, and concluded that postvaccinal encephalitis is not likely to be due to modification of any known virus. Modification of a known virus, if such occurred, might of course explain the histological picture, which is not that associated either with lethargic encephalitis or poliomyelitis, and certainly not with that following intracerebral inoculation of vaccinia.

While, therefore, the characteristic histology of fatal cases of encephalitis, following vaccinia, smallpox and measles, etc., remains the chief argument for the view, which I personally share, that some common latent virus declares itself under the stimulus of another virus infection, we still lack the knowledge of the nature of this unknown virus. The disseminated scleroses, acute and chronic, approach most closely these postviral encephalitides in histology, but their ætiology is unknown, as is that of encephalitis lethargica, which possesses a totally different histology and does not come into the present picture. Yet there are already encouraging signs that the position is not likely to remain hopeless, and one of these encouraging signs is the realization that if one likely animal does not react to a suspected virus, another animal, however unlikely, may do so. We have seen that the yellow fever virus can infect some species of monkey and not others, while, by a happy chance, it has been found to infect mice with ease. So also does the neurotropic virus of of louping-ill. We are now informed that the severe outbreak of encephalitis which occurred at St. Louis in America last autumn and is still the object of intensive experimental investigation, is communicable readily to mice, while in monkeys it produces only a febrile condition that may be missed unless careful examinations are made. Sera from cases of the St. Louis disease neutralize this virus, but not sera from cases of lethargic encephalitis, of which many have been tested. Doubtless we shall hear much more about this matter before very long. I should also note that Sabin (1934) has recorded the recovery of a virus readily communicable to rabbits from a fatal case of the ascending Landry type, following the bite of an apparently normal monkey and associated with the presence of necrotic foci in certain abdominal viscera. This interesting virus is being further investigated at the Lister Institute by Dr. Sabin.

The prospects of ultimately unravelling the ætiology of what are often no more than symptom-complexes referable to disturbances in the central nervous system—may I allude just to epilepsy and cysticercosis—are by no means discouraging, and it would seem highly desirable to lose no opportunity of investigating to the full any likely material that offers itself.

I would also refer to the very rare risk of generalized vaccinia following

vaccination, and to the recent valuable report by Dible and Gleave (1934) on a case of this kind. The virus of vaccinia was in this case recovered from the pocks, but not from the brain, in which there was a complete absence of lesions. Another case of this kind, reported by Weichsel (1931) in a child aged 17 months, had severe involvement of the central nervous system, with left hemiplegia, following the general eruption, but survived with residual spastic hemiparesis. The writer expressed the view that the condition was one of postvaccinal encephalitis, accompanying generalized vaccinia. The virus was not recovered from the blood or vesicle fluid. I am not aware of any other alleged cases of postvaccinal encephalitis having been accompanied by generalized vaccinia.

Administrative practice.—I would conclude with some remarks on vaccination practice, rather a static question in spite of the argument devoted to it, perhaps because of the argument devoted to it.

At our discussion in 1929 I pleaded for the continuance of infant vaccination on an entirely voluntary basis, but supported and encouraged by the fullest informative propaganda explaining what vaccination means and what benefits it is calculated to confer. Infant vaccination is rarely, if ever, followed by postvaccinal nervous disturbance, while re-vaccination, a necessary part of any vaccination scheme, is easily borne at later appropriate periods. The greater local and general disturbance following primary vaccination of young adults and the greater danger of postvaccinal encephalitis, more especially when mass emergency vaccinations are carried out in face of smallpox, need no emphasis. May I just refer to a recent outbreak of smallpox at Malmö, in Sweden, which occasioned the vaccination of 87% of its inhabitants, and was accompanied by five cases of postvaccinal nervous disturbance and much trouble and worry over sore arms, so much so as to necessitate a special report to the International Health Office on the staphylococci present in the lymph used.

In the course of the discussion here in 1929 Sir Francis Freemantle commented on the effect on international relations and on commerce and trade if it were known that this country had abandoned even a defective system of compulsory vaccination. Dr. Millard agreed that compulsory vaccination was no longer justified, and so did Dr. Garrow. Dr. Copeman believed it would be an advantage if vaccination came under the purview of the public health authorities, and so into line with other immunization measures for prevention of disease.

Professor Greenwood thought the danger from lack of vaccination was not serious, provided that the means of adequate vaccination could be mobilized without delay. In the discussion at the Brighton Congress in 1932, Dr. Forbes agreed that the present system must go, and be replaced by a purely voluntary system. If, he said, vaccination were optional, the parent would consider the advantages and disadvantages with an unbiased mind, and to enable him to make up his mind he would have the fullest informative propaganda not now available to him. The Swedish experts strongly recommend vaccination in early childhood, but they do not seem to have decided whether such vaccination should be compulsory or voluntary.

Dr. A. F. Cameron (1932) has expressed himself as opposed to indiscriminate hospitalization of mild smallpox cases, a point on which I too ventured to comment, as also did Dr. Garrow. The vaccination experts in Sweden also advocate increased educational propaganda. In spite of the fact that the Association of Public Vaccinators at their meeting in 1933 predicted the most lugubrious results if compulsory vaccination went—and with it the public vaccinators—I think it is fair to say that the bulk of responsible opinion would favour the abolition of the compulsory element and the placing of vaccination on a free and voluntary basis, beginning with the infant, and repeating at school age and early adult life, such system to be supported by a widespread educational crusade as for all other immunization procedures of proved benefit to the individual and the community.

REFERENCES

"Smallpox in Alexandria," *Off. Int. d'Hyg. Pub.*, 1933, xxv, 1559.
ALLARIA, *Boll. Sez. Ital. Soc. Microbiol.*, 1932, iv, 560.
AMIES, *Lancet*, 1932 (ii), 558; 1933 (i), 1015.
ASSOC. PUBLIC VACCINATORS, *Pub. Health*, 1933, xlvii, 29.
CAMERON, *Pub. Health*, 1932, xlvi, 50.
CHAPIN and SMITH, *J. Prev. Med.*, 1932, vi, 273.
DIBLE and CLEAVE, *J. Path. Bact.*, 1934, xxxviii, 29.
EAGLES and LEDINGHAM, *Lancet*, 1932 (i), 823.
EAGLES and KORDI, *Proc. Roy. Soc.*, 1932, B. iii, p. 329.
EAGLES and MCCLEAN, *Brit. J. Exp. Path.*, 1931, xii, 97.
FORBES, *J. Roy. San. Inst.*, 1932, liii. 142.
FLATAU, *L'Encéphale*, 1929, xxiv, 619.
GETZOWA, STUART and KRIKORIAN, *J. Path. Bact.*, 1933, xxxvii, 483.
GINS, *Zbl. Bakt.*, Orig., 1933, cxxvii, 77 (Suppl.).
GOODPASTURE, WOODRUFF and BUDDINGH, *Amer. J. Path.*, 1932, viii, 271.
GOODPASTURE, *Science*, 1933, lxxviii, 119.
GOODPASTURE and BUDDINGH, *Science*, 1933, lxxviii, 484.
HURST and FAIRBROTHER, *Brit. J. Exp. Path.*, 1931, xii, 17.
LEDINGHAM, *Lancet*, 1931 (ii), 525.
MARSDEN and HURST, *Brain*, 1932, lv, 181.
NAUCK and PASCHEN, *Zbl. Bakt.*, Abt. I. Orig., 1933, cxxviii, 171.
PETTE, *Münch. med. Woch.*, 1927, lxxiv, 1409.
REDLICH, *Wien. klin. Woch.*, 1927, xl, 344.
SABIN, *J. Exp. Med.*, 1934, lix, 115.
STEVENSON and BUTLER, *Lancet*, 1933 (ii), 228.
WEICHSEL, *Monatschr. Kinderheilk.*, 1931, xlix, 28.

The President said that the Section was particularly fortunate in having had as the first speaker Dr. Monckton Copeman, who had played, in earlier years, such an important part in the matter, and had been particularly interested in the suggestion, which he hoped speakers would deal with, that the question should again be brought before Parliament. He (the President) felt that he was now decidedly in the minority in still holding to the view that vaccination should be compulsory. He felt inclined to sympathize with something that he had recently read in a German publication [1] to the effect that the Prussian Minister of the Interior had issued an order that all anti-vaccinationist societies, including those existing among medical men in Prussia, were forbidden, as well as all public anti-vaccinationist activities. One reason why he still believed in compulsory vaccination was the present comparative absence of smallpox in Europe; in some countries such as Bulgaria, Czechoslovakia, Jugoslavia, Austria, and Hungary, according to the last Epidemiological Report of the League of Nations (1933, xii, 209) there were no cases of smallpox at all, while in many other countries the disease was no more than sporadic. That state of things he considered to be due to the enforcement of vaccination. He was aware that the type of the disease now encountered in this country, variola minor, was very mild; also that it was said that suitable measures could be taken if the more severe form happened to be introduced into this country. The question was as to whether such measures would be taken in time. Members would remember the s.s. "Tuscania" incident, [2] and the epidemic which sprang from two neglected cases on board that ship; there were 53 cases, and the mortality of the epidemic was very high. There were also severe outbreaks, though small, in Willesden in 1926, and in Hendon in 1927. For those reasons he held to the need for the continuance of compulsory vaccination.

England was not alone in having this mild type; from 1921 to 1926 there was a similar mild outbreak in Switzerland, and, strange to say, in the German-speaking part of Switzerland vaccination was not compulsory, and there was a good deal of smallpox there, mostly mild, though there were some severe cases in Basle. In the French-speaking part of the country, however, where vaccination was compulsory, there were comparatively few cases. Also, an outbreak of the mild type occurred in the island of St. Miguel in the Azores in 1923.

[1] *Deut. med. Woch.*, 1934, lx, 260.
[2] *Ann. Rep. Chief. Med. Off. Min. Health*, 1928, 109; *Brit. Med. Journ.*, 1929 (i), 874.

The question of encephalitis was one of extraordinary interest, and one which he had followed ever since the first accounts of it appeared. It was first prevalent in 1924, but isolated cases of the condition were recorded before that date. There was no doubt that vaccination was causally connected with it, though at first such connection was doubted. It was now generally accepted that vaccination was at least one factor. It was essential that its extraordinary rarity should be realized. He had not seen an instance of it, though he had read many descriptions. Though Dr. T. F. McNair Scott [1] had collected 22 cases in the first year of life, it was very rare in that first year, and hence there should be no hesitation about vaccinating in the first year of life. Encephalitis after re-vaccination was likewise very rare, but some cases had been recorded. As Professor Ledingham said, there was still much mystery connected with the subject of encephalitis. For example, why was it that the neuro-vaccine used by Levaditi in Spain in over two million cases did not cause encephalitis, yet when brought to Holland it caused many ?

Professor Ledingham had mentioned the subject of intracutaneous vaccination, about which a good deal had appeared in the literature lately.[2] Many clinicians favoured that method, the chief reason apparently being that it did not leave a scar. The objections made against it were that it was more painful, that the technique was more delicate and more difficult to carry out, and that it did not protect from encephalitis afterwards. In comparison with encephalitis, all the other complications of vaccination were insignificant.

Dr. E. W. Goodall said that with regard to the encephalitis which had been observed in connection with vaccinia, it should be remembered that this sequel was known to follow most of the acute infectious diseases of this country, and especially smallpox, varicella, measles and mumps. Whereas, however, it had, in his experience, been very rare before the Great War, it had increased in frequency—though it was still comparatively rare—since that event. The late Dr. Acland had, before the War, investigated, on behalf of the Royal Commission on Vaccination, a large number of cases of disease alleged to be induced by vaccination, and to the best of his (the speaker's) recollection, there was not a single case of encephalitis amongst them. He had referred to the Great War, but he ought rather to have said the great pandemic of influenza of 1918-19, the magnitude and importance of which had been overshadowed by the closing phases of the War. He agreed with Sir William Hamer in the view that there was some connexion between extensive and severe epidemics of influenza and certain affections of the central nervous system, and he also agreed with Professor Ledingham, whom he understood to say that the nervous sequel was due not so much to the virus of vaccinia as to some unknown factor the activation of which was aided by the vaccinia virus.

With regard to compulsory vaccination, he was not inclined to throw away a weapon which might be useful at some future time, should variola major again visit this country. That was not at all an unlikely event, seeing that that form of the disease was at present prevalent in a land so near as Egypt. Those who advocated the repeal of the compulsory vaccination Acts stated that they would rely upon persuasion to forward vaccination, but the slow adoption of immunization against diphtheria did not promise much success for reliance upon persuasion, at any rate in this country. He admitted that the means adopted by sanitary authorities of recent years in the case of a few outbreaks of variola major, especially the following up and observation of contacts, had been successful, but it remained to be proved whether they would be equally efficacious, in the absence of vaccination, if variola major were to gain a footing in this country.

[1] *Brit. Journ. Child. Dis.*, 1930, xxvii, 245.
[2] *Med. Annual*, 1931, 502 ; 1934, 518.

Dr. J. A. H. Brincker said he would like to have particulars of the preparation of the flocculating serum concerning which Professor Mervyn Gordon had quoted Craigie as saying it raised the hope that smallpox contacts might be passively immunized with a reasonable expectation that the disease would be aborted, even where vaccination might fail to prevent actual infection.

It was a great satisfaction to him that Dr. Monckton Copeman was also favouring the idea of getting rid of the compulsory aspect. He (the speaker) as an officer in public health administration, had been coming more and more to that conclusion. The human being was a peculiar and complex individual, and when you wanted him to agree to do anything, his psychological outlook on life had always to be borne in mind. We were all agreed that smallpox could only be prevented by vaccination, but people must be given the opportunity to think for themselves on the question. As Dr. Monckton Copeman had well said, since vaccination was now in the hands of Public Health Authorities, they had the opportunity of dealing with it in a perfectly scientific manner and the question of people submitting themselves voluntarily to vaccination should be carefully considered

Professor Ledingham had said that there was no agglutination relationship between varicella and smallpox; but he (the speaker) would like to know whether Professor Ledingham could explain—perhaps by biochemical means—why variola minor was so different from variola major. He (Dr. Brincker) suggested that there was some biochemical factor in connection with the evolution of the disease which rendered it, in the milder form, so much milder. Whilst the toxic properties of the latter had been largely lost the pocks of the disease had also become more superficial; were these changes due to some biochemical factor or not?

With regard to diphtheria immunization, a toxoid was now in general use, as this had a better immunizing effect and at the same time did not produce the toxic properties of diphtheria; was that because a certain part of the diphtherotoxin had been eliminated by the chemical effect on it of formalin, etc., and if so, could a similar explanation apply to the differences between variola major and minor?

In the experiments to which Dr. Monckton Copeman had alluded, a disease at first generalized became, after passage through animals, a local disease. He hoped that Professor Ledingham would be ready to explain these points when, in the near future, another discussion took place on the same subject.

Dr. R. P. Garrow said he had been much struck by the remark of Dr. Copeman to the effect that the question arose, when faced with an outbreak of so-called mild smallpox, or variola minor, whether vaccination should be insisted on, or whether the visitation should be allowed to "rip." One of the features of this mild disease was that it would not "rip"; it had not the power to do so. In other words, it was incapable of spreading furiously through the community and causing death or disfigurement, or even of causing serious inconvenience by a high incidence.

In a certain district in the Midlands about ten years ago it was discovered that about thirty or forty cases of mild smallpox existed, and the question arose what action should be taken. It was decided to "wait and see," in other words, to "let it rip"; no further cases occurred. Mild smallpox would not "rip."

If members of the profession were to have any view at all, whether modern or not, on the subject of vaccination, there must be a clear distinction between the so-called "mild" form of the disease and variola major.

Professor Ledingham had said he had arrived at the conclusion that variola minor was a fixed variant of smallpox. He (Dr. Garrow) asked what was a "fixed variant" of disease. Were not all infectious diseases fixed variants of something? It was true that they were not all so closely related to one another as were variola major and minor. Diphtheria and scarlet fever were not so closely related as, for instance, typhoid and paratyphoid. It was clear that there were different degrees of

variation. When it was possible to say that a particular disease was a fixed variant of another, he suggested that, for all practical purposes, it was a different disease. That had been so generally recognized now in the case of variola minor that a separate name had been given to it. But in this country, though the dual view had prevailed in the literature of the disease, nevertheless the position still was that the official figures were presented to the medical profession and to the public as if both were one disease. Therefore it was not possible to tell whether the deaths recorded were from one or the other. That represented very well the state of confusion in which the subject remained. If one thought of vaccination in relation to variola major, there was no need for any change in the view of the profession. Vaccination was the means of controlling the disease, and was the best example of prevention which had been devised. But with regard to the conception of the disease as seen in variola minor, he felt inclined to agree with those who preferred to have the mild disease rather than submit to vaccination.

Another matter which occurred to him in connection with the recent epidemic of smallpox in this country, was that it was constantly pointed out to those who had the mild disease in their district that efficiently administered districts had none. London was then constantly being held up as being so efficiently administered that the disease had not any hold.

A different story must now be told, however. London, like any other town in which the disease had been well introduced, had undergone a good "salting," and neither vaccination, isolation, nor any other measure, had succeeded in stamping out the disease. And, though the country, as a whole, was free from smallpox, London was still presenting from six to twelve cases each week.

It was necessary, in arriving at a view on vaccination, to make a clear distinction between the major and the minor disease.

Dr. Monckton Copeman (in reply) said he had been asked whether the secondary vesicles in generalized vaccinia could be shown to contain material of a living nature. During his official career he had had to investigate a few cases of this form of the disease, instances of which were very rare, for out of many thousands of cases of vaccination which he had had to inspect, he only saw four or five of these. But in each of them he removed material from the secondary vesicles, and had it tested at the Government station on calves. From the scientific point of view it might be of interest for members to be told that in each single instance he and his colleagues were able to carry on the disease to the calf by such inoculations, showing, therefore, that the secondary vesicles contained the living virus of the disease, just as much as did the original vesicles at the point of vaccination.

He was extraordinarily interested in what Dr. Mervyn Gordon said about the work of Dr. Buist, of Edinburgh. Apparently Buist did stain and see the minute virus bodies.

He would like to refer to a lengthy Report on the Histology of Vaccinia, probably the most extensive one which had appeared in English on this subject. It was by the late Professor Gustave Mann and himself, and it was presented by the speaker and his colleague to the Government in exchange for having it reproduced, with numerous photographs, in the Annual Report of the Chief Medical Officer to the Local Government Board for 1902. There was a disadvantage that the Report was "buried" in the official volume. An inspection of the photographs in association with the descriptions would show that, under the term "Z granules," there were presented beautiful pictures of the minute bodies which were now generally known as the elementary (Paschen) bodies of the disease.

He thoroughly agreed with what Dr. Goodall said about encephalitis; apparently that complication had no existence in this country earlier than ten or twelve years ago. In his earlier days at the Local Government Board, a good deal of inspection

was carried out in relation to vaccination; he visited hundreds of public vaccinators, and saw records of many thousands of vaccinated cases, and he always made a special point of inquiring into any secondary troubles. His work of this nature terminated before the date which had been mentioned, but in all his experience he did not meet with, or have reported to him, a case which could be interpreted as a possible case of postvaccinal encephalitis. It seemed clear, therefore, that this was quite a recent complication.

Something had been said about letting the milder form of the disease "rip"; it was a tentative idea which originated with the chief medical officer of the Health Authority in Portugal, as furnished in a report to the International Bureau. What was meant in that report was, that the mild disease should be allowed to take its course; that it was unnecessary to vaccinate, seeing that while the mortality was negligible, the effect of the disease on the people made vaccination unnecessary, the benefits of the latter being secured without opposition. He had had to investigate outbreaks in which this mild disease did spread to a considerable extent, and went on for perhaps weeks, and here and there occurred a case of what appeared to be the more severe form of the disease, only with the difference which Dr. Brincker had pointed out, that there seemed to be a practical absence of toxicity in the case, even though the whole body might be covered with the coalescing lesions. In certain of these instances, after the initial outburst, the disease came to a rapid and satisfactory termination. That had a bearing on the treatment of smallpox as it was appearing in this country at the present time.

With regard to the lesson conveyed by the outbreak which originated in the "Tuscania," it should be borne in mind that it was still possible, now that air travel was becoming so universal, that importation of cases of the virulent disease from such countries as Egypt and India might occur from time to time. The disease in this country now, however, was wholly of the mild type, in connexion with which there was definite question as to whether equally good results could not be obtained by merely adopting suitable sanitary precautions as by the usual measures of vaccination and isolation, which necessarily involve considerably more expense.

Dr. Mervyn Gordon (in reply) said that the experimental serum about which Dr. Brincker had asked was prepared by Professor Tulloch by immunizing rabbits against a virulent strain of vaccinia virus. Professor Tulloch observed how much protection he could get by giving falling doses of it to rabbits, and found that he could get such good protection experimentally with this serum that the Medical Research Council suggested in the introduction to the joint report by Craigie and himself [1] that these experiments raised the hope that eventually it might be possible to apply passive immunity to smallpox contacts; so that even if vaccination was carried out too late to prevent an attack, the temporary protection afforded by such serum would tide the patient over until the active immunity produced by vaccination came into operation.

Professor Ledingham (in reply) said he was sorry that the President and Dr. Goodall still considered that vaccination should remain on a compulsory basis. He (the speaker) had changed his opinion on that matter. Two factors had had an influence in his change of attitude on the question: one was the occurrence of cases of postvaccinal encephalitis, and the other was the fact that all the smallpox now in this country was of the mild form. He would urge the adoption of propaganda to ensure the vaccination of children at the earliest period of life, when the danger from untoward effects of vaccination was minimal. As the President had said, postvaccinal encephalitis was certainly a rare risk, but its importance was not to be

[1] *Med. Res. Council Spec. Rep.*, No. 156, 1931.

measured by its rarity; as a matter of fact about a thousand such cases had been recorded to date. He did not attach much importance to the statement that neurovaccine was employed in Spain without being associated with encephalitis, while following its use in Holland such cases occurred, because these accidents were so liable to be overlooked unless careful inquiry was made. Italy, for example, until recently was thought to be free from such sequelæ of vaccination. His opinion was that further legislation on the subject of vaccination was long overdue, an opinion shared by Sir George Buchanan, who also considered that vaccination should be on a voluntary basis and that it should be "little and often." That would not be secured until people were told what vaccination against smallpox meant and what benefits it is calculated to confer.

He wished he could answer the question as to the essential difference between variola minor and variola major, and to what the difference was due. The difference had been recognized in the United States for thirty years, and in that country there were still outbreaks of the virulent type, especially on or near the Mexican Frontier. That would always happen, and it might happen in this country.

In answer to Dr. Garrow, as to the nature of the mild smallpox (alastrim), he (the speaker) certainly considered that experience had shown it to be in all probability a fixed variant but it was impossible, as yet, to explain how it arose. There were, however, analogies with virulent and non-virulent races of bacteria possessing different serological affinities and in certain virus diseases, e.g. foot-and-mouth disease, the existence of serological types was well recognized. With the recognition of the actual virus elements responsible for these pock infections, the way was now open for the more accurate study of virus races from the serological and other points of view.

Section of Otology

President—W. J. HARRISON, M.B.

[*February* 2, 1934]

Palato-pharyngo-laryngeal Paralysis as a Complication of Thrombosis of the Lateral Sinus.—W. M. MOLLISON, M.Ch.

Walter B., aged 16, was admitted to Guy's Hospital on November 1, 1933, with symptoms of left acute mastoiditis and a swelling in the upper part of the anterior triangle of the neck. Operation performed. Pus was found in all the cells, and the lower part of the lateral sinus was roughened. Anti-streptococcal serum was given on two occasions. Five days later, on account of a rigor and rise of temperature to 105° F., the sinus was further explored and opened; pus was found. An attempt to ligature the internal jugular vein was abandoned, on account of extensive infiltration of the tissues around the carotid sheath, but pressure in the wound upwards caused pus to well up into the opened lateral sinus. The patient was extremely pale and anæmic. Serum and mercurochrome were given intravenously on two occasions, and later a blood transfusion was carried out. Recovery followed, and the patient was discharged on December 13.

On November 2, the day after the first operation, difficulty in swallowing developed, and it was found that the left side of the soft palate was paralysed, as were the left side of the pharynx and the left vocal cord. The patient regained control over swallowing in three or four days, but the paralyses remained though they were less marked.

Politzer gives references to five cases of the condition; of these I have only been able to find

(1) *Case quoted by Stacke and Kretschmann* (1884).

Patient, a man, aged 35. Left suppurative otitis media. Rigors, headaches. Operation. Difficulty in swallowing noticed the same day; tenderness along internal jugular; hoarseness, dyspnœa and finally aphonia. Death three days after operation. Post mortem, lateral sinus and internal jugular vein were found filled with soft clot; subdural abscess in middle fossa.

(2) *Case published by Ludewig* (1890).

A girl, aged 17, had influenza. Left acute otitis media; spontaneous perforation; three weeks later, rigors. Mastoid operation: four days later, paralysis of the soft palate, so that fluids returned through the nose; three days later the paralysis had disappeared; four days later the patient died.

Post mortem, in the region of the jugular foramen destruction of the wall of the sinus was seen to have occurred over an area of 2 c.mm.

Discussion.—Mr. HERBERT TILLEY said he had never had experience of "associated paralysis" following suppurative inflammation in the ear; but at a meeting of the Section of Laryngology he had shown a male patient who had pachymeningitis involving the right jugular foramen, associated with paralysis of the corresponding vocal cord, palatal and pharyngeal muscles and the sternomastoid and upper part of the trapezius muscles.

Mr. CHARLES BENEY said that a fortnight previously he had had a case which seemed to him worth recording. The child was five years of age and had had measles in December, from which it recovered. On Christmas Day both ears began to discharge. On admission to hospital the patient was desperately ill. A week before admission the mother noticed that the child could not walk properly and would not eat.

On admission to hospital there was paralysis of the palate and pharynx—it was impossible to be sure about the larynx, but the voice was altered and the speech slow. There was marked spasticity of all the limbs and on attempting to walk, the child fell over. Apart from the palato-pharyngeal paralysis the central nervous system was normal. The cerebrospinal fluid normal. A swab was negative to Klebs-Loeffler bacillus. There were no definite signs of mastoid involvement.

At operation, the mastoid was found to be necrotic and full of pus; the lower part of the lateral sinus was unhealthy, but was left alone. A wide area of dura was exposed and the temporo-sphenoidal lobe explored in many directions without finding pus.

On lifting the dura, a small quantity of gas escaped. A paracentesis was performed on the opposite side.

Three days later the paralysis and spasticity had disappeared. For a few days there was a gelatinous discharge from the ear operated on. The child is making an uninterrupted recovery.

Mr. T. H. JUST said that he also had had a case with similar symptoms which came on after operation. It was a case of lateral sinus thrombosis, with the clot spreading down towards the bulb. The sinus was opened and packed firmly. Signs of involvement of the eleventh and twelfth nerves and of raised intracranial pressure came on after operation. These cleared up rapidly on removal of the pack, showing that they must have been due to pressure in the region of the jugular foramen.

Two Cases of Unsuspected Fractures of the Base of the Skull.—HAROLD KISCH, F.R.C.S.

(I) I. C., a boy, aged 17 years and 10 months, was sent to hospital by his doctor on account of discharge from the left ear and pain in the head, on 25.9.33.

History.—Two weeks and four days previously he had fallen from a diving board on to paving-stones; he did not lose consciousness, and went home as usual. In the evening there was some watery discharge from the left ear, and this discharge was somewhat red next morning. He had had discharge from this ear when 11 years old, and again one year ago.

On examination.—Purulent discharge; anterior-inferior perforation of the drum. Hearing diminished a little on the left side, but bone conduction normal. No nystagmus; labyrinthine reactions normal.

X-ray report.—V-shaped fracture of the posterior fossa. One arm runs into the petrous bone, and the other into the left mastoid process.

Recovery uneventful.

(II) S. S., widow, aged 61, came to hospital 18.12.33, complaining of bleeding from the left ear.

On 12.12.33, she fell from a tram on to her buttocks, but did not hit her head in any way. She went into the London Hospital, where she was receiving treatment for varicose veins, but did not mention the accident. She felt a little shaky, but otherwise no discomfort until 16.12.33, four days later, when she had a curious feeling in the heart and blood gushed out of the ear. There was an "awful" noise in the ear, and she was unable to hear with it. Two days later she came to hospital.

On examination a little blood-clot was found in the meatus; no perforation in the drum could be seen, but there was a scar in the posterior quadrant. Hearing was reduced in the left ear (watch, 2 in.) but there was no indication of injury to the labyrinth. A skiagram taken some days later showed a fracture of the petrous portion of the left temporal bone. Recovery was uneventful. The X-ray reports are by Dr. Graham Hodgson.

I am showing these cases partly because of a discussion which took place here in which considerable doubt was thrown on the use of X-ray examination in the diagnosis of fracture of the skull. In the two cases I now show I do not think the certain diagnosis could have been made in any other way.

Discussion.—Mr. RITCHIE RODGER said that sometimes radiological examination was unreliable. Two months ago a case of injury had been passed on to him by a surgeon, because a little swelling had developed behind the ear. The radiological examination had not revealed any fracture. The presence of a meatal discharge, with tympanic perforation and mastoid swelling, indicated the need for mastoid operation. He (the speaker) made the incision for exposure a little longer in the upward direction, and saw a fracture, 1½ in. long, running up into the squama; he did not elevate the periosteum further than was necessary. There was infection of the mastoid process, beginning at the lower part of the fracture. He performed the mastoid operation as gently as possible, so as not to disturb the fracture, and an excellent recovery ensued.

Mr. P. J. JORY asked why Mr. Kisch had had a skiagram taken of the case if he did not suspect a fracture.

The PRESIDENT said that skiagraphy was often useful in detecting such fractures. He did not think that one ought to declare that a certain method was of no use generally because in one or two cases it did not prove to be so. He had had cases of fracture of the base to operate on, and had found X-ray examination useful in some; this at times gave a good idea of where the fracture was, and the condition the surgeon was up against.

Mr. KISCH (in reply to Mr. Jory) said that fracture of the skull had not been suspected before the cases were seen by him.

Recovery of Hearing after Serous Labyrinthitis and Apparent Complete Loss Seven Months Previously.—F. C. W. CAPPS, F.R.C.S.

G. E. H., aged 22, was admitted to hospital May 10, 1933 with acute suppurative otitis media on the left side, of six weeks' duration.

He had been treated elsewhere by syringing, but was referred to me as he did not appear to be making satisfactory progress and had on that day begun to vomit and felt giddy.

On examination.—Copious discharge from left ear from an attic perforation; a typical fistula sign. There was an old radical mastoid cavity on the right side; the operation had been performed when the patient was eight years old. Temperature, normal; pulse 85.

Operation.—May 11, 1933.—The mastoid cavity was filled with pus and necrotic bone. The cranial sinus and the dura of the middle fossa were exposed. There was cholesteatoma in the antrum and aditus. Part of the bridge was removed, exposing the floor of the aditus, and a typical fistula into the semicircular canal was then seen. The cavity was widely opened, packed with bipped gauze and allowed to heal by granulation.

When the hearing was tested before discharge the patient was found to be stone deaf in the left ear, both by air and bone conduction. There was no longer any fistula sign and a cold caloric test produced no reaction on the left side.

The patient was well except for slight giddiness until November 1933, when he had an attack of erysipelas starting from the right ear and spreading across to the left. He was seen at hospital again on December 20, with a recurrence of pain in the left ear, and a temperature of 99°. He had a large furuncle and general otitis externa which developed into a typical erysipeloid cellulitis.

He was admitted to hospital, and the condition in the left ear gradually cleared up, the inflammation in the meantime proceeding across to the right side. The focus of infection would appear to have been a crack in the right external meatus.

The patient is now quite well but the attic perforation is still moist. To my

surprise, on recovering from the above condition, he again had definite hearing in the left ear. He now hears Bezold's forks from 90 upwards and up to 20 cm. by air conduction on the monochord. A cold caloric test by cold-air douche gave a normal reaction after 70 seconds.

Mr. LIONEL COLLEDGE said he recalled a case in which erysipelas had taken a peculiar course similar to that in this instance. The patient, a middle-aged man, had had a radical operation performed on the left ear, followed by erysipelas from perichondritis on the left side. This crossed his face to the right ear, which swelled up, and it tracked round the back of the head to the left ear, which again swelled. Then it crossed his face and the right ear swelled again. After going twice round the head and halfway back, the erysipelas had died away on the back of the head.

With serous labyrinthitis one might expect hearing in a patient who had simply had an ordinary Schwartze operation performed for acute middle-ear suppuration. A girl, aged 16, had nystagmus and all the signs of acute labyrinthitis following operation. Sir Charles Ballance saw the patient with him (the speaker) and thought nothing operative should be done. Ten days afterwards the nystagmus had disappeared, and the patient ultimately had perfect hearing.

Bilateral Tuberculous Mastoiditis.—F. C. ORMEROD, F.R.C.S.

Edith W., aged 25. Previously shown February 1931.

Attended Westminster Hospital, January 1928. Had had operations on both mastoids two years previously. Right ear dry and healed. Left ear discharging with granulation tissue. February 1928: left mastoid reopened; necrosed bone and granulations removed. June 1928: left radical mastoid operation; giant cells found in granulation tissue. Post-aural wound broke down. Several operations to clear granulation tissue and to close wound during 1928-29. During 1930 empyema of the maxillary antrum developed: antrum drained intranasally. January 1931: right ear recommenced to discharge and the post-aural wound broke down; left ear still discharging. At this point patient was exhibited at a meeting of the Section. X-rays showed recent absorption of bone on right side and sequestra on left side. February 1931: right radical mastoid operation with removal of large area of necrosed bone. Post-aural wound left open; healed by epithelialization with wide post-aural fistula. May 1931: removal of further necrosed bone and granulation tissue from left ear. Similar operations July and August 1931, January and September 1932, and February and July 1933. On the last occasion a flap of the posterior meatal wall was stitched back to the skin of the back of the pinna and the ear became dry during October 1933 with an epithelialized fistula.

The case is shown as an example of the persistent formation of granulation tissue and of new bone which very rapidly became necrotic. There have never been any signs of pulmonary phthisis.

The hearing in the left ear is very slight, as far as air conduction is concerned, and there is normal bone conduction. Hearing is improved in the right ear if the post-aural opening is kept plugged with cotton-wool. The patient's hearing is better after inflation with the eustachian catheter or after Valsalva's manœuvre—a phenomenon often found with dry radical mastoid cavities.

Discussion.—Mr. SOMERVILLE HASTINGS asked whether the organism was actually found in this case, and if so, whether it was of the bovine or the human type. Nowadays he saw very few cases of tuberculous mastoid, certainly fewer than he met with twenty years ago. He asked whether that was the general experience.

Mr. H. V. FORSTER said he would be glad of Mr. Ormerod's advice about a case of subacute otitis media in a pulmonary tuberculous subject, a colleague of his. He had subacute middle-ear disease on the right side, with a drum which was intact but remained congested. Was it right to perform an exploratory puncture or a paracentesis? There was no pain now, though a little had been noticed two or three weeks ago.

Mr. ORMEROD (in reply) said that the tubercle bacillus was not found in this ear; the case was diagnosed by the presence of giant cells. He had never, in such cases, been able to find the bacillus in the granulation tissue in the mastoid.

In Mr. Forster's case he would puncture and draw off some of the fluid from the middle ear; he would not make an incision. As in the case of tuberculosis in the larynx, if the chest was improving the larynx generally improved too; so would the ear in this case. He would advise doing as little as possible at present.

Seven Patients illustrating Alleviation of Deafness and Tinnitus by the Zünd-Burguet Electrophonoïde Method.—G. C. CATHCART, M.D.

All of these patients have suffered from chronic catarrhal otitis media; four, in addition, have had suppurative otitis media, and one has had a radical mastoid operation. All of them have had the usual classical methods of treatment, which have failed to do any good with regard either to the deafness or to the tinnitus.

B. T. = before treatment and A. T. = after treatment. V. = my ordinary conversational voice, which normally can be heard at a distance of 80 feet, and Wh. = my whisper after deflating the chest, which normally can be heard at a distance of 20 feet.

Master F. L., aged 12, seen April 1933. When 2 years old, discharge from left ear; this dried up. Deaf since then. Operation for tonsils and adenoids when aged 3 at Gray's Inn Road Hospital and again last year at Fitzroy Square Hospital.

	Left ear	Right ear
B. T.	V. 6 ft., Wh. nil ...	... V. 12 ft., Wh. nil
A. T.	,, 18 ft., ,, 1 ft.	... ,, 25 ft., ,, 1 ft.
Second T. Jan. 1934 ...	,, 20 ft., ,, 1 ft. 6 in.	... ,, 30 ft., ,, 1 ft. 6 in.

Tinnitus ceased after first course.

Mr. D. T., aged 19, seen January 1929. Operation for glands in neck at age of 9 months; measles at age of 6 years; always deaf since. Tonsils and adenoids operation at 15; perforation and débris in left ear, and most of drum gone in right ear; both ears dried up under the treatment.

	Left ear	Right ear
B. T.	V. 15 ft., Wh. nil ...	... V. 2 ft., Wh. nil
A. T.	,, 80 ft., ,, 6 in. ...	... ,, 10 ft., ,, 3 in.
Third T. Jan. 1934 ...	,, 35 ft., ,, 1 ft. ...	... ,, 14 ft., ,, 4 in.

Tinnitus ceased after first course.

Mr. J. B., aged 38, August 23, 1930. Some years ago Mr. C. Heath had blistered the drums and this had made the deafness worse than it was before.

	Left ear	Right ear
B. T.	V. 8 ft., Wh. 2 in. ...	... V. 6 in., Wh. nil
A. T.	,, 35 ft., ,, 4 in. ...	... ,, 8 ft., ,, at ear
Second T. Jan. 1934 ...	,, 40 ft., ,, 4 in. ...	... ,, 18 ft., ,, ,, ,,

Tinnitus ceased after first course.

Mr. H. P., aged 43. Since infancy has had discharge and deafness in the right ear. At 7 years had mumps, and the left ear, which was very deaf before, became much worse, and remained so until he had the Zünd-Burguet treatment. At 20 had radical mastoid operation on right ear, and was almost completely deaf after it. Then went to learn lip-reading, as he was told he would become completely deaf. At 23 had Zünd-Burguet Electrophonoïde treatment, which improved his hearing to such an extent that he abandoned learning lip-reading, and during the War he was passed B2 for the Army. He had constant tinnitus for many years, which was cured by the Zünd-Burguet Electrophonoïde treatment and has never returned.

	Left ear	Right ear
B. T.	V. 1 ft., Wh. nil	... V. 1 ft., Wh. nil
A. T.	,, 6 ft., ,, ,,	... ,, 10 ft., ,, ,,

Tinnitus ceased and has never returned.

Second T. ...	V. 8 ft., Wh. nil.	... V. 16 ft., Wh. nil
Third T. ...	,, 12 ft., ,, ,,	... ,, 20 ft., ,, ,,

Mrs. R., aged 44, seen October 1927. Deaf for 17 years; had abscess in left ear some years ago; seen several aurists; told nothing could be done.

	Left ear	Right ear
B. T.	V. shout at ear, Wh. nil	V. 4 ft., Wh. nil
A. T.	,, 3 ft. ,, ,,	,, 16 ft., ,, at ear
Second T. Oct. 1930	Noises not come back and hearing gone back only a little	
Third T. Jan. 1934	V. 4 ft., Wh. nil ...	V. 20 ft., Wh. at ear

Tinnitus ceased after first course.

Miss H. D., aged 58, seen January 1932. Deaf several years; interfered with pianoforte teaching three years ago, when she also lost her sense of pitch.

	Left ear	Right ear
B. T.	V. 3 ft., Wh. nil	V. 2 ft., Wh. nil
A. T.	,, 30 ft., ,, at ear	,, 15 ft., ,, at ear
Second T. Jan. 1934	,, 30 ft., ,, ,, ,,	,, 15 ft., ,, ,, ,,

Tinnitus ceased after first course and sense of pitch was restored.

Mr. J. W. M., aged 59, seen October 1933. Deaf for some years. In June very severe cold in head and deafness became much worse; ears syringed and then buzzing set in and has remained ever since.

	Left ear	Right ear
B. T.	V. 12 ft., Wh. 9 in. ...	V. 1 ft., Wh. nil
A. T.	,, 35 ft., ,, 6 ft. ...	,, 18 ft., ,, 6 in.

Tinnitus still present but less.

It is to be noted that in all these cases there was tinnitus. In one the tinnitus has been alleviated only, and in the others it has been cured—i.e. a percentage of 85 cures in these cases of tinnitus treated by this method.

Discussion.—Mr. CHARLES BENEY said he believed that he had been the second person in London to get an electrophonoïde instrument. He had treated many patients in this way, with some startling results, but also with a number of disappointments, and during the last year or two he had been less inclined to use it, as the results did not seem to justify the labour of the treatment.

Mr. THACKER NEVILLE said that he had used the treatment, having been taught how to do so by Mr. Cathcart. He had found it of value. For example, he had had a patient who was going to be married in a week and had troublesome tinnitus, which, however, was of recent origin. It was cured in three treatments. Another patient had about forty treatments and her hearing was improved.

Mr. E. H. RICHARDS, whilst acknowledging with gratitude continued help and encouragement from Mr. Cathcart, said that he had had no appreciable results either in deafness or in tinnitus in a series of cases in which active "catarrh" had been excluded. The criterion was testing with the whispered and spoken voice. A noticeable feature in Mr. Cathcart's series was that the nasal symptoms subsided as the hearing improved—in some this was apparently due to recent operation. He wondered whether the Zünd-Burguet vibrations might possibly relieve nasal "catarrh."

Mr. J. ACOMB said that he had the apparatus and had seen it worked in Paris by M. Zünd Burguet. After a year's work he had had very discouraging results and he could only remember one patient being distinctly benefited. The method did, however, alleviate tinnitus.

Mr. R. SCOTT STEVENSON said that he had used this apparatus for ten years, but he now only employed it in conjunction with eustachian catheterization. Sometimes patients were not improved by the apparatus and improved by eustachian inflation, sometimes they were improved by it and not by eustachian inflation. The word "alleviation" of deafness used by Mr. Cathcart should be emphasized; the method did not cure deafness. Rather more than half the patients he had treated with it had improved to a certain extent; some were not improved at all, and even those who had improved had to come back for further treatment. There was no exact scientific method yet of estimating the hearing, so that testing by the voice should not be scorned; he had found some patients changed from a negative to a

positive Rinne after treatment. Until there was some more exact method of testing than tuning-forks or the audiometer, it was of no use to rely on anything but the capacity to hear the human conversational voice, which was what the patient wanted. With this apparatus he did not really think there was any question of re-education; it was a mild oto-massage, which, in conjunction with eustachian catheterization, helped a certain proportion of people who had chronic otitis media.

Mr. J. F. O'MALLEY said he would like to see a case of the usual type of middle-ear trouble, diagnosed under that name, treated by middle-ear inflation, or, if necessary, by oto-massage of the drum, and see what result ensued; then, having ascertained that, to see what the electrophonoide method would do. During the last month he had had a case of the type which would improve if treated by this method, just as it had improved after treatment by inflation and oto-massage. When examined a month ago the patient was Rinne-negative, and a whisper could not be heard at a further distance than 2 ft. On the day of the treatment, however, quiet conversation could be heard and a whisper at 15 ft. When seen a few days ago the patient was Rinne-positive. He (the speaker) thought the old-fashioned methods should first be tried, and when these had improved the hearing as far as possible, this instrument should be used, and, if it carried the improvement further, special credit could be given to it. He feared that none of the available methods of testing were exact.

Mr. W. STUART-LOW said that the apparatus had certainly, in these cases, relieved the tinnitus—that bugbear of otology. He had questioned the patients, and all admitted improvement in their general health, and a more hopeful outlook, as they felt that something tangible was being done for them. In some of the cases the hearing had been improved. And simply the fact that they slept better made the apparatus worth while. Such results as these should be brought to the notice of nerve-specialists, who then might send these difficult cases to the otologist.

Mr. CATHCART (in reply) said that all his patients stated that the treatment made them sleep better. He had kept one patient at the head of a very large business for ten years by this treatment. Formerly he came once or twice a year, now he came three times a year for ten days, not because of deafness, but because the treatment gave him satisfactory sleep in the intervals.

As the patients knew nothing about this possibility, he (the speaker) maintained that the good effect which this method of treatment had on so many cases of deafness and tinnitus was a physiological, not a psychological, one.

Complete Stapes thrown off during Chronic Suppurative Otitis Media, ? Tuberculosis.—W. J. HARRISON, M.B. (President).

Mr. T. had returned from a Sanatorium in Switzerland in March 1933, and was still confined to bed when I was asked to see him on account of deafness, and distressing tinnitus in the right ear. Four to five years previously this ear had discharged for a short time. At the time of examination there was no discharge and the membrane was intact.

I did not see him again until he came to consult me on 13.11.33 with the following history:—

In May, without any pain, the ear had begun to discharge a thin, watery, rather offensive fluid. He had occasionally had pain of a shooting character in the mastoid at night. He had been syringing his ear with boric lotion and instilling drops (his doctor informed me these were 50% spirit). When he was using the syringe on 10.11.33, a "piece of bone" came away, which he brought to me, and I found it to be the stapes shown.

Examination showed complete destruction of the membrane and ossicles, and the inner wall of the middle ear covered with granulations. There was slight tenderness over the mastoid. Hearing had deteriorated rapidly after the discharge appeared, and the ear is now quite useless: AC−, BC−, Rinne−.

He was leaving Northumberland to live on the South Coast in a few days and he did not come to see me again.

W. S. THACKER NEVILLE, F.R.C.S.Ed., showed the following instruments:—

(I) **Well's Electric Iodine Vaporizer.**

Thirty grains of powder, consisting of iodine, boric acid, camphor, menthol powdered cubebs, each 4 per cent, with thymol 1 per cent, are placed in the electric heater. The current is turned on. As soon as the heat reaches a sufficient degree, a cloud of smoke emerges from the outlet tip and this can be pumped through a catheter into the middle ear.

(II) **Fowler's Auto-Insufflator.**

To inflate the ear, insert into one nostril, close the other and blow up the balloon.

(III) **Lester's Pneumo-tympanic Masseur.**

Insert into the ear. Squeeze rubber ball. If this is attached to a Siegel's speculum, the tympanic membrane will be seen to move in and out.

[*The report of the Discussion on Chronic Catarrhal Otitis Media will appear in the next issue of the* Proceedings *of the Section*].

Section of Radiology

President—R. S. PATERSON, M.D.

[*January* 19, 1934]

The Protracted-fractional X-ray Method (Coutard) in the Treatment of Cancer of the Larynx

By J. H. DOUGLAS WEBSTER, M.D., F.R.C.P.E.

(*From the Radiological Department, Middlesex Hospital*)

IT will always be worthy of record in medical history how Butlin and Semon, about 1890, revived the discredited operation of laryngofissure, and how in the hands of Sir StClair Thomson, Sir James Dundas-Grant, Moore, Tilley, Colledge and others, this operation has had a wonderful record of success up to about 75% of cures in early selected intrinsic cases. Unfortunately, when the extent of the disease is more advanced, or when the histological grade of the malignancy is high, laryngofissure often proves an incomplete operation, being followed by a high percentage of recurrences, for which the only surgical treatment (apart from radium-surgery) is total laryngectomy, with its high operative mortality, its serious mutilation, and its risk of recurrences.

Further, in epilaryngeal malignant disease, surgical treatment usually proves a failure, and this is so in spite of the advances made in this region by Trotter and others. There is, therefore, much room for improvement in the possibilities open to pure surgery in cancer of the larynx, and radiological methods are becoming more and more worthy of serious consideration.

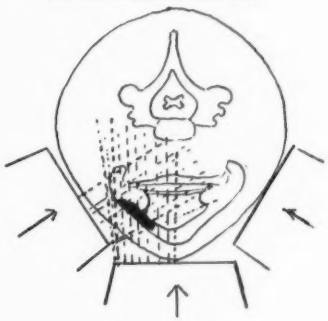
Even in the early days of deep X-ray therapy occasional apparent cures were recorded. For instance, Sheppegrell reported a case (histologically proved) in which the patient was greatly benefited by a course of daily treatments over twenty days. He had a marked reaction, both local and general, but when this subsided the intralaryngeal tumour had disappeared and there was left only some infiltration of the left vocal cord. Following a further treatment this thickening also disappeared, and his voice improved greatly.

However, when deep X-ray therapy came into more general use, cases of damage to the skin and cartilages were soon recorded. In a number of these the damage was probably due to an entirely wrong technique having been used. Many radiologists followed for the larynx a technique similar to that sometimes advised for the thyroid gland (in exophthalmic goitre) consisting of three fields, one anterior and two lateral. This is a bad technique, I believe, but it is one which appears in the textbooks. That this was wholly wrong is shown by Table I. By this method of cross-fire a double dose is given in the thyroid cartilage just at the place where, as Hautant has pointed out, the cartilage is most sensitive—the anterior-inferior angle of the ala. He has excised this portion in a series of cases with or without neighbouring growth before the radiation treatment, to prevent necrosis.

Table I (fig. 2) shows the method of water-bag and wax building up the surface, so as to cross-fire with the production of a skin erythema, and 100% depth dose through the larynx.

TABLE I

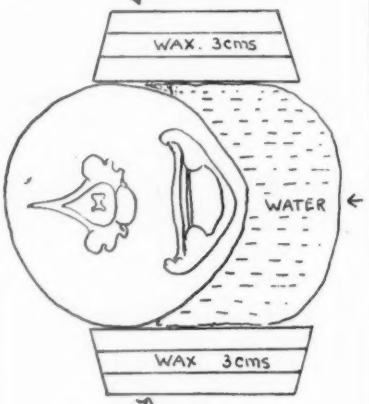
Fig. I — A 3-Field Method



Not adopted.

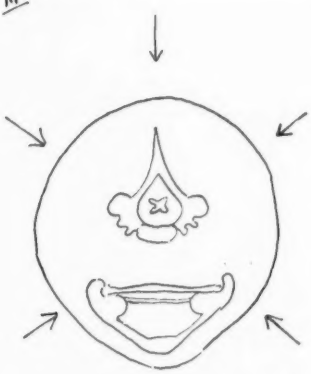
Bad technique - risk of cartilage-damage - maximal dose anteriorly.

Fig. II — Method (1)



(Lateral dose took 75')

Fig. III



Method (3) ↑ Finzi's Method

1922-3 (1) Wax + waterbag method
± 100% in larynx in 2-3 days.
abandoned for :-

1924-30 (2) Simple or multiple crossfire
(Similar dosage)

1931 (3) Finzi's Method - 6 field
1 case in 1927: 6 cases in 1931.
± 240% in larynx in 12 days.
abandoned for:-

1932 (4) Holfelder's Method
cross-fire: 2 lateral fields
± 320% in larynx in 14 days
or

1933 (5) Coutard's Method: cross-fire. 2 or more lateral or oblique-lateral fields. ± 600% in 14-28 days.

Fig. 3 shows Finzi's method with approximately 240% dose in the larynx within twelve days (erythema dose, according to Levitt's publication of St. Bartholomew's Hospital technique). In 1927 one case, and in 1931 six cases, were treated with Finzi's method with such unsatisfactory results that the method was abandoned for Holfelder's and, later, for Coutard's.

My study of 42 cases of cancer of the larynx treated with X-rays shows clearly that cancer in this region can rarely be controlled by methods of X-radiation which have so often been successful in other sites, such as the skin, uterus, and breast. All methods of mild radiation, and the so-called "massive" dose within a few days, have ultimately led to failure, except occasionally in post-operative "prophylactic" cases in which it is unknown if any malignant cells have been left or not.

In inoperable cases more encouraging results have been found after the dosage has been highly fractioned, divided over three or four weeks, and particularly when the total dose has reached a very high total intensity—up to six or more of the milder "skin erythema" doses. (See Table VII, at end of paper.)

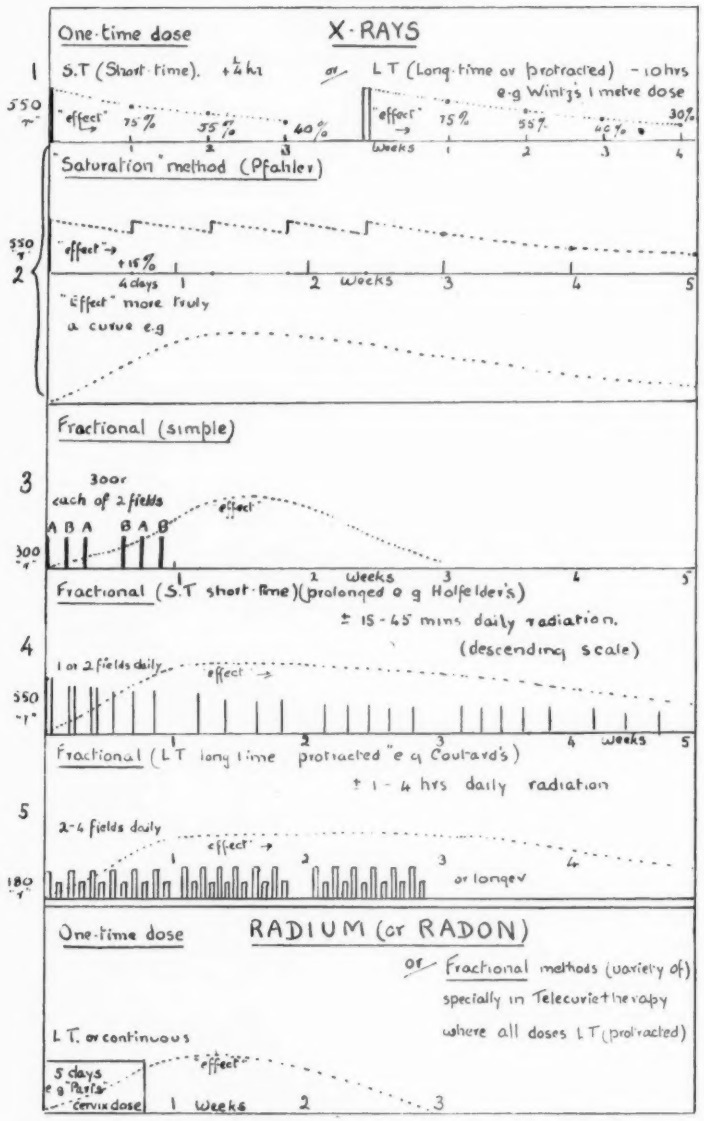
In Table II (p. 26) can be seen the various possible radiation doses with X-rays or radium, either continuous or discontinuous. It will be seen as the table is followed down that the schemes of X-ray fractional radiation more and more closely approximate to methods of radium therapy, and indeed this is the most striking characteristic of Coutard's method of protracted-fractioning—its similarity to radium treatment.

In my outlook on X-ray treatment of cancer of the larynx I find I have passed through five or more alternating phases of hopefulness or discouragement.

The nine cases treated in 1922-23 were treated with the method of building up the surface of the neck with water-bags and plastic wax and radiating by cross-firing so that a 100% erythema dose (so-called "Erlangen Dose") was given throughout the larynx. Except in one or two post-operative cases this method entirely failed. As an example may be given the case of patient "J." After a partial laryngectomy, with removal of one cord and part of the thyroid cartilage, he had radiation by this method given within a few days. Following this, in about two months there was a recurrence. Total laryngectomy was performed, and the histological report of the growth then was that it was very cellular and active: i.e. as a result of the incomplete operation, or the X-rays, or the two combined, the growth appeared to have been stimulated to greatly increased activity.

As a result of this failure of the "Erlangen method" I was sceptical, for long, as to the possibilities of X-ray treatment in this type of malignant disease, and for the next seven years simple methods of cross-firing were adopted, e.g. in simple cases two-field cross-firing, or when the glands were enlarged two or three treatment fields on the affected side and one on the more healthy side. In most of these cases, although an apparently adequate dosage of 100% was given within a few days, total failure can only be recorded from this period. In 1927 one patient was treated with an adaptation of Finzi's method, going round the neck in six fields. No effect was found in this case, an advanced one of epilaryngeal cancer with ulceration and glands. In 1931 I made a further trial of Finzi's method. The case was a subglottic cancer, the histological type rather resembling some parotid gland tumours. A high tracheotomy was performed. Within one month 6 by 16% and 12 by 33% were given. This had a good result for over a year and a half, when the patient had a recurrence, for which he was treated with the one gram radium unit. Further recurrence followed six months after the radium treatment, and the patient has been treated lately, after a low tracheotomy, lower down in the trachea, with deep X-rays, which has again led to marked improvement of signs of obstruction. The patient unfortunately, however, has X-ray signs of metastases in both lungs. One case after laryngofissure in 1931 remains well, following a five-field course of X-rays. The other four patients, treated in 1931 by Finzi's method, or a five-field modification of it (missing out the posterior field), showed little or no benefit.

TABLE II



In 1932 I decided to treat three pyriform fossa cases—one inoperable, and two recurrent cases—with a more prolonged method of fractional radiation, based on the technique used by Holfelder (Table III).

These three patients were treated within a period of four to six weeks with daily doses—in all, with total surface doses of 600-620%. The inoperable case showed healing of an extensive ulceration of the left arytenoid fold, but only temporarily. One recurrent case, after operation and application of radium, showed healing of aryepiglottic ulceration, and his doctor wrote that he was well a year afterwards. The third one failed. So that this method had two failures to one apparent success; it seemed to be a doubtful method.

Last summer I had the opportunity of treating two laryngeal cases. One was an old personal friend of my own, and it was because I wrote to Coutard asking for his advice in the treatment of this patient that I adopted Coutard's technique in these two cases with, so far, apparently successful result.

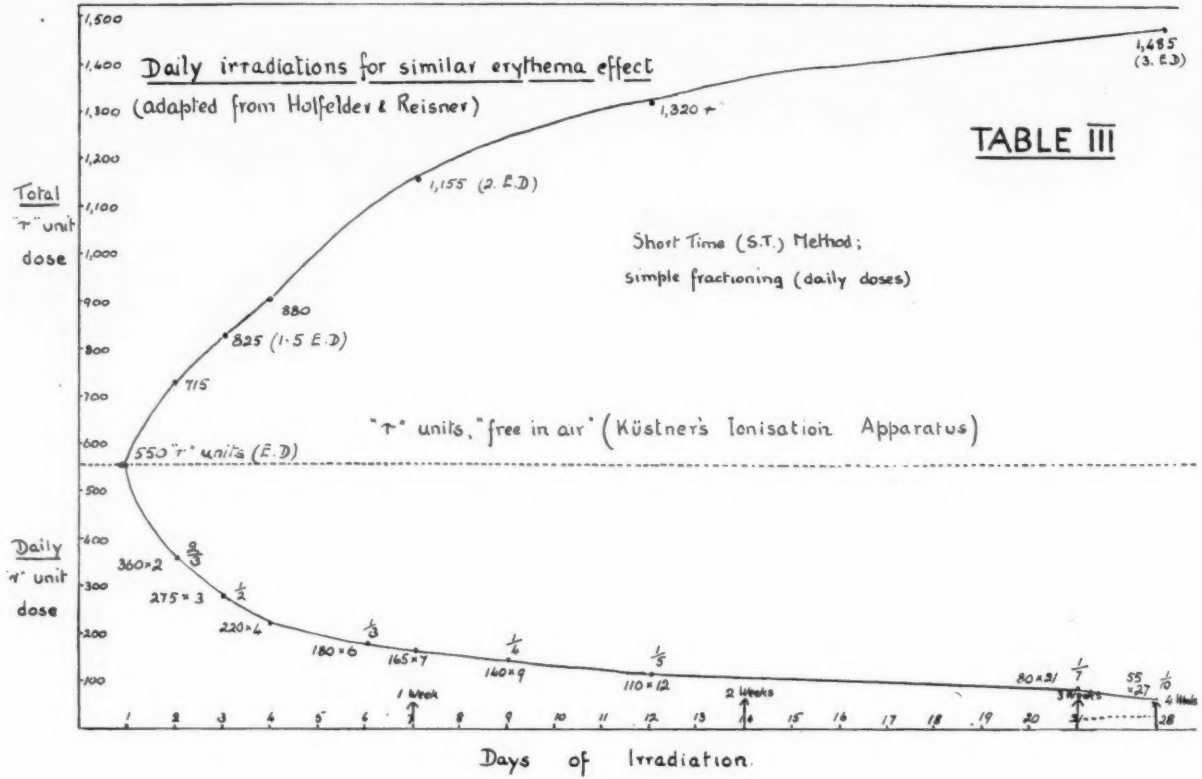
As each patient treated by Coutard's method will be found to demand an expenditure of time and energy equivalent to that of about 20 patients treated by the more usually adopted methods of "short-time" radiation, it is with some misgivings that one embarks first on a trial of it.

The first case treated last year had a first course by a fractioning method whereby in twelve days (eight treatment days) he had 16 by 20% cross-firing on the larynx. This was a man who had refused operation and radium treatment and had been sent to me by Mr. F. J. Cleminson. He had a large fixed mass over the right side of the larynx and œdematous swelling of the right arytenoid and false cord. By direct laryngoscopy a section was taken from close to the right false cord, but the tissue removed was only œdematous; another section was taken from the external tumour and showed an undifferentiated squamous-celled cancer with much fibrous reaction. The total dose he had by the first method adopted was 1,760 *r*; according to Holfelder's Table (Table III) this was a very full dose within the time of treatment. But this "short-time" course had little or no effect on the size of the external swelling or on the laryngoscopic appearances, and as the patient was going down-hill, with swallowing difficulties, I resolved to supplement this first course by a "long-time" treatment according to Coutard, and accordingly I treated him in twenty-two days (nineteen treatment days) with an additional 4,770 *r*, a total of 6,530 *r*, a quarter of which had been given with four-minute doses, and three-quarters of which had been given with the protracted dosage of fifty-seven minutes for a dose of 180 *r*. During the course of the protracted-fractional radiation the external swelling became reduced in size and the treatment was stopped with the appearance of the fibrinous reaction in the mucosa. The external tumour soon disappeared, and the patient, seen a week ago, shows no signs of recurrence, more than six months after the treatment,[1] though there remains some œdema of the right arytenoid. I feel convinced that without the additional protracted-fractional doses, this patient would now be dead.

In the meantime the other patient for whom I had asked advice from Coutard, was undergoing treatment. He was a patient for whom total laryngectomy had been advised by an eminent laryngologist, but the patient refused this, and partial laryngectomy was performed by another surgeon, the left vocal cord and all the visible growth being removed. The pathological findings were Grade 3 in Broders' classification, so there was, most will agree, from this point of view alone, a considerable possibility of recurrence.

Coutard wrote that he should have "at least 6,000 *r* in not less than fourteen days and not more than thirty days." Beginning treatment four weeks after the operation I gave him in twenty-eight days (twenty-four treatment days) 6,030 *r* as a total dose, equally divided on the right and left sides of the neck. As the airway was rather narrowed owing to part of the anterior commissure having been removed, Mr. Cleminson performed a low tracheotomy before the radiation began. The

[1] Condition remains the same in May 1934.


Daily irradiations for similar erythema effect
(adapted from Holfelder & Reisner)
TABLE III
Short Time (S.T.) Method;
simple fractioning (daily doses)
"r" units, "free in air" (Küstner's Ionisation Apparatus)
Total "r" unit dose
Daily "r" unit dose
550 "r" units (E.D)
715
825 (1·5 E.D)
880
1,155 (2. E.D)
1,320 r
1,485 (3. E.D)
360×2
275×3
220×4
180×6
165×7
140×9
110×12
80×21
55×27
1 week
2 weeks
3 weeks
4 weeks
Days of Irradiation.

rubber tube did not interfere with the radiation. The usual swelling and discomfort appeared, together with the early fibrinous reaction of the mucosa. The tube was removed after two months, having been in position for about three months.

Neither of these two patients treated by Coutard's method shows, at the present time, any sign of recurrence, just over six months after their treatment finished.[1] It is of course far too short a period in which to claim anything in the nature of a cure, but at the same time laryngeal cancers very often show recurrences within a short period of months, and most of my patients showed a recurrence within much less than six months.

Of my series of 42 cases (shown in summary in Table VII), nearly half were cases of primary inoperable growths (19), while one had refused operation and radium (total laryngectomy probably would have been required), one advanced case came after failure of surface radium treatment, and 10 were post-operative "prophylactic" cases; the remainder all had recurrences after operation with or without supplementary radium treatment. Twelve of the series had intrinsic laryngeal cancer (one was subglottic); the greater proportion were extrinsic, and 10 of these were pyriform fossa cases. Histologically grouping them, one recurrent case had columnar-celled carcinoma, the subglottic patient had a growth resembling a parotid tumour, while most of those with histological reports had squamous-celled carcinomas, of skin or mucous types, in various grades of malignancy. A further possible intrinsic type is basal-celled carcinoma. In the epilaryngeal region the radiosensitive types of the lympho-epithelioma of Regaud, the transitional-celled carcinoma of Cutler and lymphosarcoma may be met with.[2]

My study of this series leads me to suggest that those who advocate any other method of treatment than the protracted-fractional method of Coutard should produce their complete results in support of their methods, for the only method I know of which can show convincingly good results, after long periods of years, is that of Coutard, and its value has also recently been confirmed by the results of a number of other radiologists, for example, Schinz and his collaborators Kahlstorf, Zuppinger and Stewart-Harrison, at Zürich. Holthusen in 1930 analysed his 44 cases of cancer of the larynx, with the result that he found, as I did, that practically 100% had been failures. Holthusen therefore adopted Coutard's method in 1930, and in the last three years has had a large percentage of apparent cures. My analysis of my cases clearly appears to lead to the same conclusion, and I propose to treat future cases by Coutard's method, or by intensive fractional methods such as Holfelder's.

As regards the general value of the method for laryngeal cancer: in a recent record Schinz has summarized the following opinion: With an intrinsic laryngeal cancer of the mucosa type or where there is little or no differentiation, Coutard's treatment is the treatment of choice. In cancer of the true cord of the skin type, Coutard's method is to be recommended when the cord is still movable; but if the growth is of the skin type and is of a larger extent operative measures are to be recommended, or a trial of Coutard's method. In all epilaryngeal cases Schinz recommends Coutard's method as the method of choice.

Turning to the biological, clinical, and technical sides of Coutard's method, one of the most important points to realize is that Coutard's lowering of the *r* per minute intensity has made the total dose which can be safely given rise steeply. This can be well seen in the table adapted from Holthusen, whereby it is evident that when the radiation intensity is reduced to about 2 or 3 *r*/min. the total dose which can be given may be increased to three or more times the dose which can be given safely with "short-time" methods. (See Table IV, Fig. 1.)

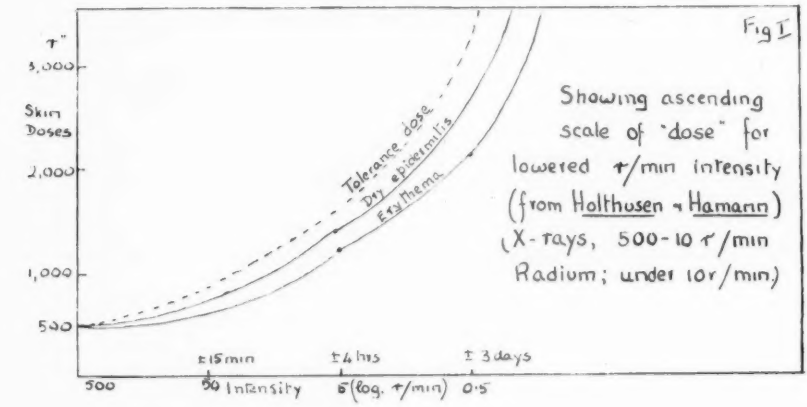
It was the experimental work of Regaud and his colleagues on the effect of

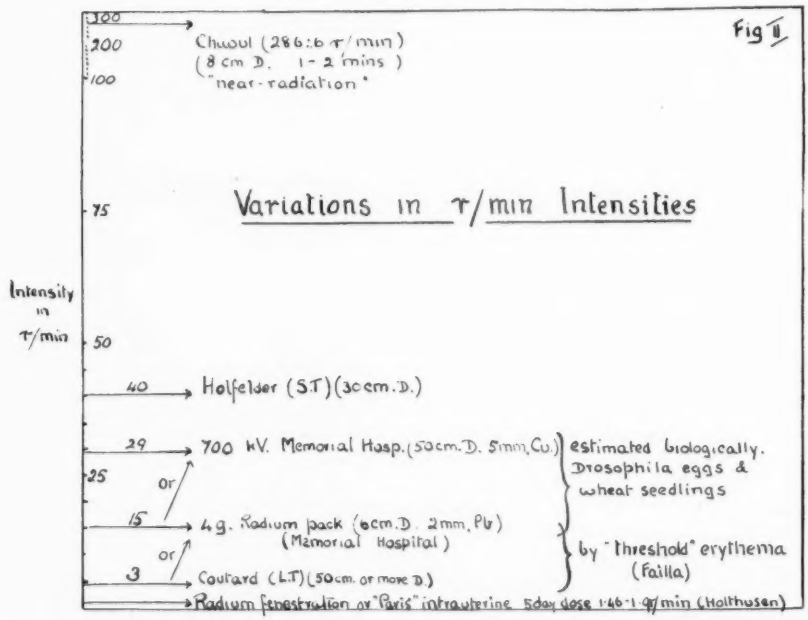
[1] Both still appear well at almost twelve months.

[2] Dr. R. W. Scarff has recently reported histological details of nearly 700 cases of squamous-celled carcinoma from the Middlesex Hospital (upper air-passages).

fractional radiation on the testicular germinal layers which led to this important modification of X-ray methods. This biological work in Paris has been confirmed in Zürich by Schinz and Slotopolsky. It will be remembered that the "massive" dose

TABLE IV





theories of Krönig and Friedrich, and of Seitz and Wintz, were based on the skin reactions as shown by erythema, i.e. they were blood-vessel reactions. Regaud took up the alternative position that the effect of radiation on malignant tissue was much

more likely to be demonstrated by the study of the effects of radiation on continuously multiplying cells, such as the testicle germinal cells, and his experiments show that on these cells fractional radiation has a much greater effect than "one-time" massive doses. He showed also that the fractioning increases the interval between the skin and the growth radio-sensitivities, so that by fractional dosage, while little or no effect on the skin might be produced, a great effect might be produced on the testicular cells. This theory has been adapted to clinical research in cancer by Coutard, with brilliant results.

The value of the protracting (low minute-intensity) has not been so closely analysed as the value of the fractioning, but recent experimental work of Zwerg has been valuable in showing that the protracting produces a minimal vessel damage, and also minimal damage to the blood, lungs and kidneys in comparison with fractional short-time treatment with similar total intensities.

The five essentials in Coutard's method of treatment may be summarized as follows:—

(1) The use of high voltages (180 or 190 kv.), filtration by 1·5 to 2 mm. of copper or zinc, skin focal distance of 50 or more cm., and two directly opposing lateral fields, with or without supplemental fields on the affected side (in extensive pharyngeal growths, in patients with marked adenopathy, or in patients with very thick necks).

(2) Each dose must be *protracted*, i.e. must have a low minute-intensity as compared with ordinary X-ray treatment technique. Coutard's choice of degree of protraction gives doses which per minute are 10 to 20 times weaker than the doses given by the usual methods. Thus, for example, 150 or 180 *r* will be given in 50 or 60 minutes (3-4 *r* per minute, not 30 to 40 *r* or more, as is often given). (See Table IV, Fig. 2.)

(3) The doses are *highly fractionated* (as compared with other fractional methods). Thus at least two daily doses are given, for example, one for an hour in the morning and one for half an hour in the afternoon, with the exception of Sundays; and the doses are divided up over two, three, four or more weeks: the larger the area involved, the longer must be the total period of treatment, as the patient cannot be treated for more than three or four hours a day, if we would avoid undesirable general reactions.

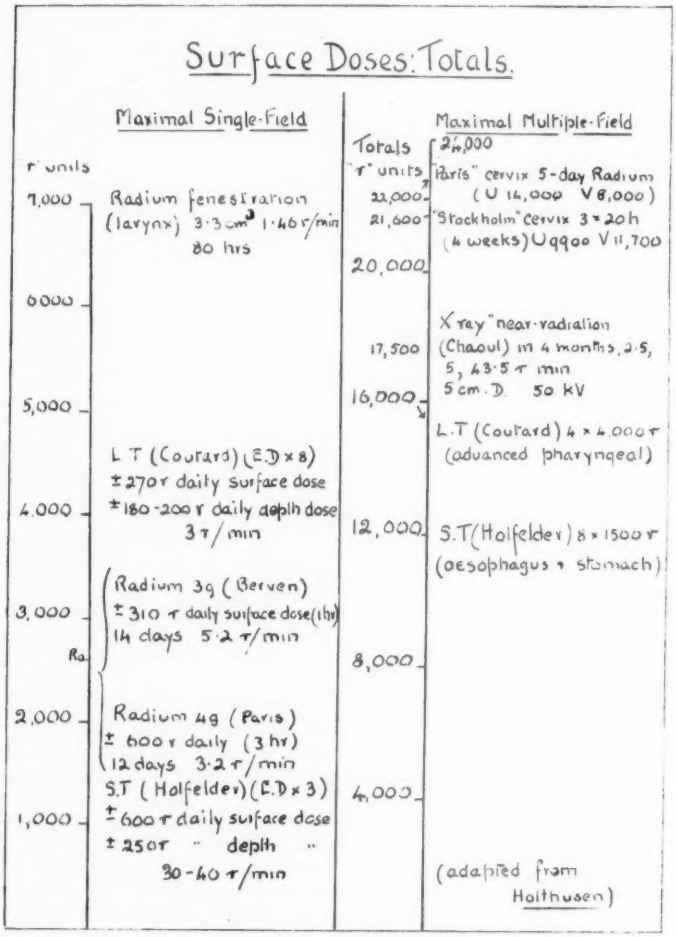
(4) An extraordinary *high total dosage* is administered (and regarded as necessary) as compared with most other symptoms of dosage: on the surface a total of 10 to 20 times the mild "erythema dose" in all may be given, and given with safety. (See Table V.)

(5) For each patient the dose must be estimated beforehand carefully, and then it must be controlled by accurate measurement of the H or, as later used, the *r* units: and further and most essentially, controlled by the appearance in the pharynx and larynx of the white fibrinous mucosal reaction, and by the appearance on the skin of an epidermitis. The radiologist must be experienced in laryngoscopic examination and should examine the patient daily to note the extent of the mucosal reaction. The skin dose given is the "epidermicidal" dose—Regaud and Nogier first described it in 1913—the effect of which is rather alarming when first seen, but soon passes away, when resulting from the given conditions, with complete repair. The patients should not be treated as ambulant cases; they must be under close supervision, as in advanced cases laryngeal œdema may necessitate a tracheotomy if this has not been performed previously.

The method is based upon clinical observation of treatment of tumours arising from different sites in the larynx—tumours either of the skin or of the mucosa type. When a dose has been sufficient to destroy the normal epithelium temporarily, a tumour arising from similar epithelium should also respond to such treatment. For instance, if a dose of about 45 H (4,500 *r*) is required for the destruction of

normal epithelium, and for the mucous membrane reaction about 35 H (3,500 *r*), then to ensure that such doses reach the level of the lesion to be destroyed, we should have to give about a double surface dose to that which we wish to give deeply on the mucosa.

TABLE V



It is easy to give a total dose of 7,000 *r* for epitheliomas of the mucosal type, but for the epitheliomas of lesser sensitivity (skin type) it is difficult to reach a total dose of 90 H or 9,000 *r* without exceptional care in the technique and administration. When Coutard's doses have reached more than 10,000 *r*, as a rule there has been no cure and damage has resulted.

Many variations of the method must obviously be adopted, according to the extent of the growth, glandular involvement, size of the neck, and whether the case is a localized intrinsic one or is an extrinsic one.

When a tracheotomy is performed previous to radiation, it should be a low tracheotomy, as Jüngling and others have reported damage to the cartilage where a high tracheotomy area has had a full course of radiation.

As to the results gained with the method, Coutard's are given in Table VI. They show a percentage of 32% (three year) of 77 cases. These results have been confirmed, as already stated, by Holthusen, from Schinz's Clinic by Kahlstorf and Zuppinger, and Stewart-Harrison and others. Hegener and Holthusen reported two years ago a number of cases, some treated by radium fenestration methods, others by Coutard's method. From Schinz's Clinic there are so far no three years' results.

TABLE VI.—EPITHELIOMAS OF THE LARYNX TREATED BY X-RAYS, 1920-1926.[1]

Results of Roentgen Therapy at beginning of 1931 after more than:

Years	2	3	4	5	6	7	8	9
Cases treated	1920-26	1920-26	1920-26	1920-25	1920-24	1920-23	1920-22	1920-21
Results	25 in 77 (32%)	25 in 77 (32%)	22 in 77 (28%)	13 in 60 (21%)	7 in 43 (16%)	6 in 31 (19%)	4 in 19 (21%)	4 in 8 (50%)

H. COUTARD. *American Journal of Roentgenology and Radium Therapy*, 1932, xxviii, No. 3.

Criticisms of the method have been made from several points of view, the first naturally being the very long time and expenditure required. As each patient needs thirty to sixty hours of radiation it is obvious that the tube expenditure must be high, and in Zürich and in Düsseldorf it has been estimated that the hospital cost of each patient must be something like £60. The time required is a further problem. I was only able to treat the two patients last summer by opening the Department for treatment about three-quarters of an hour earlier each morning while the Coutard treatments were being administered.

Wintz says that the success of the method is chiefly due to the fact that Coutard has dared to give such high doses, but I doubt if this criticism holds good when we consider the large number of cases of laryngeal damage that have been reported in the literature.

Borak, in Vienna, and Fried, have criticized the method by doubting the value of the protracting entirely. But Zwerg's experiments appear to show its great value. This is the most critical point for future discussion, and to decide it conclusively will take some years. Thus Hünermann, in Düsseldorf, treated eight patients with laryngeal cancer with simple fractional radiation of the growths. Of his eight cases, five reacted well at first, and became "symptom-free," but *all* recurred and died within six months or soon after. This result *appears* to show that the protracting is necessary, but it is not conclusive, as Holfelder and Holthusen, in the discussion following suggested that the doses given were not high enough.

Holfelder has criticized Coutard's method by saying that he tried it in laryngeal cases in 1930, but found he had no better results than those he had already achieved with his own fractioning method.

In a recent personal communication Holfelder allows me to state that in recent years he has treated 61 cases of laryngeal cancer, of which at least 33% are two or more years recurrence-free. By his present method he employs a technique by which, within a fortnight, a total surface dose of 3,600 *r* (i.e. over 600%) is given. This is a high dose for the simple fractioning method, and it is of course possible that there may be some late damage as a result.

If clinical and histological evidence in a considerable number of cases, e.g.

[1] Three-year results with 89 hypopharyrx cases (all inoperable) were 14%; with 46 tonsil cases, 26%.

Kahlstorf, Englmann and others, and the animal experiments of Zwerg are well based, then by the "long-time" protracted method there results an absolute minimum of damage to the connective tissue, the vessels, and the cartilage in the areas radiated, and therefore there is no likelihood of late damage. It is, I believe, the method of election in laryngeal cancer, with Holfelder's as the only alternative.

There is no doubt that we are now at the beginning of a really great advance in X-ray therapy, for in the hands of Coutard and others the new method has already been applied successfully to other sites than those of the larynx, hypopharynx and tonsil, for which it seems to have proved itself specially successful. Thus it has been employed extensively by Coutard in gynæcological cases, and by him and others in many other sites of cancer. For example, Schinz in a record of 43 cases of œsophageal cancer says that in 20 cases Coutard's method alone was used, and in five simple fractioning, while in 18 cases Coutard's method was applied in addition to radium locally. I have been told that all the patients treated by simple fractional methods were well for six months but in six more months had died, all with lung induration. Schinz suggests the use of Coutard's method also in inoperable cancer of the stomach, having tried it in five or more cases.

Critical consideration of the evidence that exists already in favour of this new method shows conclusively, I submit, that at least in squamous-celled carcinoma of the larynx, in pharyngeal, tonsillar and probably some other squamous-celled carcinomas, and possibly for other sites and types of cancer, it is one which gives great promise for the future usefulness of the X-ray branch of radiation therapy.

REFERENCES

Borak, J., *Wien med. Wchnschr.*, 1931, lxxxi, 1677, 1703; *Fortschr. a.d. Geb. d. Röntg.*, 1932, xlv, 397.
Chaoul, H., *Strahlentherapie*, 1933, xlviii, S. 31, *Münch. med. Wchnschr.*, 1934, lxxxi, S, 235.
Coutard, H., *Amer. Journ. of Roent. and Rad. Therapy*, 1932, xxviii, No. 3, p. 313.
Coutard, H., "Radiophysiologie et Radiotherapie," ii, fasc. 4, p. 541.
Englmann, K., *Zeitschr. f. Hals- Nasen-* usw., 1932, xxxi, S. 87 and S. 132.
Fried, C., *Strahlentherapie*, 1931, xli, S. 750.
Hegener, J., *Zeitschr. f. Hals- Nasen-* usw., 1932, xxxi, S. 35.
Holfelder, H., *Brit. Journ. of Radiol.*, 1932, v, p. 53.
Holfelder, H., Personal communication.
Holthusen, H., *Zeitschr. f. Hals- Nasen-* usw., 1932, xxxi, S. 3.
Holthusen, H., *Strahlentherapie*, 1933, xlviii, S. 15, *Strahlentherapie*, 1933, xlvi, S. 273.
Hünermann, *Zeitschr. f. Hals- Nasen-* usw., 1932, xxxi, S. 153.
Jüngling, O., "Röntgenbehandlung chirurgischer Krankheiten," 1924, S. 235.
Kahlstorf, A., and Zuppinger, A., *Strahlentherapie*, 1930, xxxviii, S. 199.
Levitt, W. M., "Deep X-ray Therapy in Malignant Disease," 1930, p. 35.
Regaud, Cl., *Compt. rend. Soc. de Biol.*, 1922, lxxxvi, p. 822.
Schinz, H. R., *Strahlentherapie*, 1933, xlvi, H. 1, S. 7.
Schinz, H. R., and Slotopolosky, B., *Ergebnisse der med. Strahlenforschung*, 1925, i, S. 443.
Stewart-Harrison, R., *Journ. Laryng. and Otol.*, 1932, xlvii, p. 725.
Wintz, H., *Strahlentherapie*, 1933, xlviii, S. 535.
Zuppinger, A., *Zeitschr. f. Hals- Nasen-* usw., 1931, xxviii, S. 521; *Fortschr. a.d. Geb. d. Röntg.*, 1931, Ergänzungsband 40.
Zwerg, H. G., *Strahlentherapie*, 1932, xliii, S. 201.

TABLE VII.

No.	Year	Initial	Sex, Age	Intrin. or extrin.	Clinical condition	X-ray method	No. of courses	Progress
1	1922	W.	F., 55	I.	Post-operative	(1) Cross-fire with water-bags and wax : 100 % depth-dose	1	Further operation : recurrence
2	„	B.	M., 62	E.	Recurrent (?). 3 yrs. previously had epith. of tonsil	„ „	3	Growth smaller inside : recurrence ; further operation : pneumonia
3	„	M.	M., 68	E.	Post-operative	„ „	1	No recurrence in 1923 ; lost trace
4	„	d'A.	M., 63?	I.	Post-operative	„ „	3	Well for 3 years ; later died of intercurrent disease
5	„	J.	F., 54?	E.	Advanced recurrent (columnar-celled)	„ „	2	No arrest

TABLE VII (*continued*).

No.	Year	Initial	Sex, Age	Intrin. or extrin.	Clinical condition	X-ray method	No. of courses	Progress
6	1923	M.	M., 51	E.	Inoperable: right-sided glands	(1) Cross-fire with water-bags and wax: 100 % depth-dose	2	No arrest
7	,,	H.	F., 39	I.	Post-operative: left cord; no glands	,, ,,	2	Well in 1931
8	,,	J.	M., 40	I.	Post-operative	,, ,,	1	Recurrence: total laryngectomy, "very cellular growth," later recurrence
9	,,	D.	M., 75	E.	Inoperable: large glands	,, ,,	1	No arrest
10	1924	H.	M., 56	I.	Inoperable: R. vocal cord; glands	(2) Simple or multiple cross-fire 100% depth-dose	5	Glands much smaller: later, no arrest
11	,,	We.	M., 74	E.	Inoperable: pyriform fossa, L. cord fixed	,, ,,	1	Terminal case
12	,,	B.	M., 53	E.	Inoperable: large glands	,, ,,	1	No arrest: (radium later)
13	,,	S.	M., 51	E.	Inoperable: R. cord fixed; glands	,, ,,	1	Too ill for more treatment
14	,,	P.	M., 59	E.	Recurrence after radium and tracheotomy	,, ,,	1	No arrest
15	,,	W.	M., 65	E.	Inoperable: had had Q. radium 5 months	,, ,,	1	No arrest
16	,,	O.	M., 47	E.	Recurrence (after total laryngectomy	,, ,,	1	No arrest
17	1925	K.	F., 47	I.	Post-operative (laryngofissure)	,, ,,	3	No effect: total laryngectomy: radium later
18	,,	D.	M., 63	E.	Inoperable (pyriform fossa)	,, ,,	2½	Swallowing easier: terminal case
19	,,	H.	M., 56	E.	Inoperable (pyriform fossa: large glands)	,, ,,	2	No arrest
20	,,	N.	M., 55	E.	Post-radium (twice) (pyriform fossa: bilateral glands)	,, ,,	2	Glands worse
21	1926	T.	M., 44	E.	Post-radium (pyriform fossa)	,, ,,	4	Jaw invaded
22	1927	W.	M., 66	E.	Inoperable: ulceration and glands	(3) Finzi's 6-field	1	No arrest
23	,,	F.	M., 68	E.	,,	(2) Tr. begun only		Terminal case
24	1928	L.	M., 52	E.	Post-operative	(2) Cross-fire	2	No arrest
25	,,	G.	M., 66	I.	Post-operative (laryngofissure)	,, ,,	1	Well in 1932
26	,,	S.	M., 56	E.	Post-operative (pyriform fossa)	,, ,,	3	Recurred: diathermy
27	,,	de G.	M., 50	I.	Inoperable (right cord fixed)	,, ,,	1	No arrest
28	1929	Br.	M., 58	I.?	Left larynx and glands	,, ,,	1	Terminal case
29	,,	Ba.	M., 57	E.	Inoperable (pyriform fossa: glands)	,, ,,	2	No arrest
30	1930	S.	F., 57	E.	Inoperable (pyriform fossa: glands)	,, ,,	2	Terminal case
31	1931	B.	M., 59	I.	Subglottic (parotid type of growth)	(3) Finzi's: later radium (1 g. unit): later (2)	2	Alive: with recurrence and lung metastasis
32	,,	F.	M., 72	E.	Recurrence after operation and radium	(3) Finzi's	3	No arrest

TABLE VII (*continued*).

No.	Year	Initial	Sex, Age	Intrin. or extrin.	Clinical condition	X-ray method	No. of courses	Progress
33	1931	C.	M., 59	E.	Recurrence after radium	(3) Finzi's	1	No arrest
34	,,	R.	M., 55	I.	Post-operative (laryngofissure)	,, ,,	1	Well in 1933
35	,,	R.	M., 56	E.	Inoperable: no glands	,, ,,	2	No arrest
36	,,	E.	M., 67	E.	Recurrent after radium (pyriform fossa)	,, ,,	2	No arrest
37	,,	Br.	M., 50	I.	Recurrent: glands	(2) Cross-fire	3	Arrested: well in Nov. 1933
38	1932	B.	M., 62	E.	Recurrent after operation and radium (ary-epiglottic ulceration)	(4) Modif. Holfelder's, 600% in 6 weeks	1	Ulcer healed: wrote was well in June 1933
39	,,	H.	M., 63	E.	Inoperable (pyriform fossa)	(4) 620%	1	Ulcer on arytenoid healed temporarily
40	,,	L.	M., 56	E.	Recurrent after operation and radium (pyriform fossa)	(4) 620%	1	No arrest
41	1933	H.	M., 57	I.	Post-operative (laryngofissure). Grade 3 (Broders)	(5) Coutard's, 6,030 *r*	1	Well: May 1934
42	,,	G.	M., 62	E.	False cord œdema: mass over thyroid cartilage (undifferentiated squamous-celled)	(4) 1,760 *r* (5) 4,770 *r* = 6,530 *r*	1	Mass disappeared: I.S.Q, May 1934

Mr. Douglas Harmer: During the last six years 178 patients suffering from cancer of the larynx have been treated by X-rays in our departments—the majority of them by Dr. Finzi and Dr. Levitt, at St. Bartholomew's Hospital, and a small number by Dr. Fairchild at Mount Vernon. The numbers are small because I have had to eliminate all those who also received radium treatments. It is necessary to emphasize that practically all these patients were considered inoperable, or were suffering from recurrences, often after repeated operations; in fact types of disease that would have been considered unfit for any treatment in most clinics. The treatment was given only with a view to palliation.

An analysis of the cases shows that 168 were suffering from extrinsic carcinomas involving the larynx, pyriform fossa, pharynx or post-cricoid region. I have not attempted to separate them into different classes because at present there is no evidence that they respond differently to X-rays. Of these, 127 are dead and 41 living. It will be noticed that only eight are free from disease, and that the longest period is three years. Thirty-three are living, with some disease present, but two only have survived for more than three years. If patients treated by surgery, radium and X-rays had been included the results would have been much better—probably twice as good—both as regards prolongation of life and total disappearance of disease. This latter group would have included many patients suffering from much earlier growths.

If we had included intrinsic carcinoma of the larynx which we treated by means of X-rays and radium, and if I had selected only the very early cases, the number of them would have been 10, and nine of them are living, at periods up to eight years. So confusion might arise if this were taken as an account of X-ray treatment of these diseases. Therefore Dr. Webster's statement, that cancer of the larynx treated with X-rays is not controllable by the ordinary methods which prove successful for cancer in other sites, is correct only if applied to truly inoperable

cancers. It would have been even better if Dr. Webster had said "they are rarely controllable," rather than "not controllable."

It has long been recognized that many forms of animal tumours can be destroyed by irradiation, but that although some of the cells in them can be killed by comparatively small doses there are others which require very much larger amounts and clinically this is exactly what has been observed in man.

Nearly all growths in the larynx, however extensive, appear to be radio-sensitive. If a full course of X-rays is given, the growths invariably shrink and usually there is more improvement in the primary than in the secondary lesions. It is common to find that as the growth shrinks the patient's symptoms are relieved. For instance, expectoration steadily decreases, pain is diminished, bleeding may be arrested entirely, the primary growth becomes smaller and dysphagia is relieved. Stridor and dyspnœa may disappear, so that tracheotomy is avoided. Also the growth in the glands may be arrested, and fungation through the skin prevented or even healed. As a result, the patient's general condition improves, weight is gained and, temporarily, he may believe that he is cured. In some of these cases the improvement is so remarkable that at first sight it appears as if the disease may have been completely eradicated. After the reactions have subsided, however, it is common to find that this is not the case. On examining the larynx one still sees indefinite thickening, frequently a persistent slight œdema of the arytenoid or of the part of the larynx which was infected is noticed. In others there may be slight ulceration which does not completely heal, or the vocal cord may remain fixed, and when the patient is questioned he complains that the swallowing and speech are not normal. Also the glands have not entirely disappeared. As in animal tumours this signifies that there are some cells which have not been destroyed. The question then arises whether a second course of X-rays should be given—many of our cases have received two full courses with comparatively short intervals—or when remnants only remain, how they should be treated. This may be very difficult to decide. Primary lesions if small and localized can often be destroyed with diathermy. Occasionally, radium needles or seeds can be inserted, but there is always grave danger that after intense ray treatments they will cause severe necrosis. Treatment of the gland remnants also presents great difficulties and gland dissections should not be undertaken lightly for fear that the wounds may fail to heal. Radium needles if heavily screened with 0·8 mm. of platinum can be inserted in certain cases. If the glands have broken down and are full of necrotic tissue they can be scraped out carefully with advantage.

It should be remembered that glands which are fibrosed and shrunk may remain quiescent for long periods.

Considering the types of growth that have been treated, there is no doubt that great benefit has been obtained, and that life has been prolonged. Without treatment such patients only survive for about six months, but after X-rays the period is doubled in about two-thirds of the cases. Fortunately, the final stages after intense irradiation are usually very rapid.

So far I have seen no evidence that these cancers can be destroyed by any form of X-rays given in a short period, say one or two days. Usually, it has been our practice to deliver the treatment in a comparatively short period—say from twelve to fifteen days—a few have, however, received treatments lasting over much longer periods. I am inclined to think that the treatments will have to be more protracted.

As regards the kind of current that should be used: My experience is that the results have certainly improved since higher currents were employed; also I believe that very heavy treatments causing severe reactions, both in the skin and inside the throat, must be given. The dangers of these treatments appear to me to have been over-estimated. An analysis of the cases shows that immediate complications are

rare and seldom serious. It is better to burn the skin than to fail to deliver an adequate dose. And the late reactions such as perichondritis and necrosis have not been met with nearly so often as we have been led to believe.

I have not noticed any appreciable difference in the results obtained with different grades of tumour; although the higher grade forms may respond quickly, they show such an inveterate tendency to metastasize, that in the end they respond badly to treatment. The lower grades, on the other hand, may respond slowly but are often arrested for much longer periods.

I am often asked why, if the results of X-ray treatments are so poor, the treatment is still advised?

Personally, I am quite satisfied that such good palliative results have been obtained that X-rays are still the best treatment for truly inoperable growths; whereas in the earlier types a combination of surgery, diathermy, radium and X-rays is greatly to be preferred. Levitt has pointed out that some of his best results with X-rays have followed an operation in which the disease had been partially removed. Here one might quote a case sent by Mr. E. M. Atkinson of Bath. It is interesting as showing the present trend of surgeons in different places.

This patient had an extensive growth in the pyriform fossa which Mr. Atkinson excised by lateral pharyngotomy. As soon as she was able to travel he sent her to Mount Vernon for X-ray treatment. On admission she still had considerable induration of the neck with indefinite glands but these gradually disappeared after the X-rays. Now, two years later, there is no evidence of any disease. It is extremely doubtful whether she would have been still alive unless she had received the X-ray treatment. I would suggest to the surgeons that they follow Mr. Atkinson's example, because I do not think that the importance of pre- and post-operative X-ray treatment is sufficiently realized at present.

With regard to post-cricoid carcinomas, the treatment requires careful consideration: It rarely happens that they can be removed successfully by any form of operation. Radium on the whole has given very poor results. At the present time deep X-ray therapy, with or without gastrostomy, seems to be the best form of treatment for most cases.

Intrinsic carcinomas of the larynx can be successfully treated by operation or radium in most instances, but when the disease recurs it may be so extensive or may involve the neck so widely that it is quite inoperable. In such an instance a remarkable palliative result may be obtained with deep therapy. Thus, a patient was sent by Mr. C. S. C. Prance of Plymouth who had had a carcinoma of the vocal cord removed by Mr. Lambert Lack after thyrotomy twenty-four years ago. The growth had recurred and completely filled the whole larynx, needing tracheotomy. Also the scar had broken down so that the growth was fungating. He was treated by Dr. Finzi in August 1932; the growth gradually disappeared—now there is no evidence of disease in the larynx, and the external wound is soundly healed.

Generally speaking, my experience is that intrinsic growths are more sensitive to X-rays than the extrinsic forms. Certainly this statement is true of the few endotheliomas and sarcomas which we have treated.

Summary.—Personally, I am quite satisfied that X-rays are of the greatest value in the following conditions:—

Extrinsic carcinoma.—Early cases: (1) Before biopsies, and as preoperative treatments (short courses). (2) After operation: full courses should be given as soon as the patients have recovered sufficiently to stand the treatment—say about ten days—to prevent recurrence and dissemination.

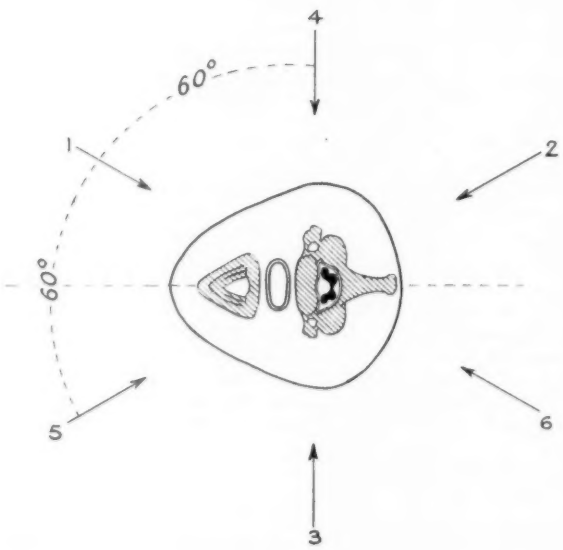
Inoperable cases: as the sole treatment. Two or more treatments often are necessary.

Intrinsic carcinoma.—In early cases: the question of pre- and post-operative X-ray treatment is a matter requiring careful consideration. In doubtful cases

when the growths have proved more extensive than was expected, particularly after laryngectomies, post-operative irradiation will probably improve the prognosis. In late cases, although we are still unable to deliver a sufficient dose to be certain of destroying the whole of the disease, X-rays still appear to afford the best treatment, and it remains to be seen whether with protracted split doses better results can be obtained.

	Treated	Dead	Living: Free from disease >1	1	2	3	Disease present >1	1	2	3	Total living
Carcinoma, extrinsic and post-cricoid (inoperable)	168	127		4	2	2	26	3	2	2	41
Carcinoma, intrinsic (inoperable)	4	1		1			2				3
Endothelioma	3					3					3
Sarcoma	3	2				1					1
Total	178	130									48

Dr. N. S. Finzi said that, since he described it many years ago, he had modified his technique in the way illustrated in the sketch (see figure). A further modification was that he did not now deliver the total quantity in 12 doses, but spread it over from 18 to 24 doses. He liked to distribute the treatment over from four to six weeks. This method, he considered, induced a considerable improvement, and at the same time somewhat decreased the patient's discomfort. He hoped Dr. Webster was not correct, because if he was it meant that, with present arrangements and



facilities, fewer patients could be treated, until the hoped-for institute was available, with many X-ray apparatus such as Coutard had in Paris. He thought it was a question not of the number of *r* per minute, but of dosage. How many radiologists would cause the same amount of damage to the skin as Dr. Webster had shown in his cases? In the cases which Dr. Webster treated by his, the

speaker's, method, did he cause the same amount of damage to the skin, and did he give the same dose?

He (Dr. Finzi) had long been convinced of the value of the fractionated dose. When a dose was given by one treatment, it frequently happened that when the reaction came, a fortnight later, the patient had an awful time; many had septic inhalation pneumonia, terminated by death.

He was also convinced as to the great importance of full irradiation on to the tumour, and further that it was necessary to be ruthless and not to be too sensitive as to the degree of discomfort caused at the time of the application. It was necessary to obtain a severe reaction of the skin and mucous membrane. Many failures were due to insufficient dosage. Dr. Webster had quoted cases of one year's and one and a half-year's duration, as examples of success obtained by this method of Coutard when he had failed by other methods, but he failed with other methods because the dose was too small. Was Dr. Webster's 100% the same as the speaker's 100%? He feared it was not. If one was to cure a case, it was necessary to get a severe skin and mucous membrane reaction. Dr. Levitt and he had had a number of patients who had lived two or three years, and then died. These were especially cases of extrinsic carcinoma of the larynx, and the reason may have been that the doses given were too small.

Dr. Levitt had recently, in his work on œsophageal carcinoma, again shown the importance of the "threshold dose." Dr. Levitt had used a method of treating carcinoma of the œsophagus by protracted doses, though not so long as that of Dr. Webster, but he found that by cutting down the time of the dose and increasing the intensity, he obtained much better results. He (Dr. Finzi) thought it was not a question of the period of time over which each dose was delivered, but of the actual dose of radiation delivered to the tumour. By certain methods that dose was larger than by others. If one delivered too small a dose in one day, it might not be sufficient to cause any effect; a certain amount must be delivered each day.

The question of intensity was very important and difficult; at least, he personally had found it very difficult to assess intensity. He thought that if his method was used and the dosage was put up, so that not quite the same amount of skin damage was produced as by Dr. Webster's method, but that nevertheless an equally large dose was given to the tumour by the method of six fields, an equally good result would be obtained, with less discomfort to the patient. Recently he had been trying to raise the dosage. He tried to spread it over a longer period, and that could be done in private work, but in hospital only with difficulty, as it was not easy to book a bed for five or six weeks. He would rather treat fewer cases and get better results, than attempt to deal with a large number less adequately.

Those were his general impressions as to technique in the cases under discussion. Some of his results in cases treated by this method extended back to over ten years; he had a patient who was under the care of Mr. W. M. Mollison, on account of a post-cricoid growth, whose first treatment had been ten years ago. She had been treated twice, because the growth had recurred after four months.

Sir James Dundas-Grant said that he had seen at Brompton Hospital in January 1922, a man, aged 67, referred to him by the L.C.C. He (Sir James) took the case to be one of epithelioma, and, with the rather thoroughgoing intralaryngeal forceps of which he claimed parentage, he removed the projecting portion of the growth which was, microscopically, typical epithelioma.[1]

The man then came under the care of the late Dr. Robert Knox, and made a complete recovery. He lived free from recurrence and died in 1925 from bronchitis and "old age" without "further trouble in his throat." Dr. Knox reported to the Section of Laryngology (*Proceedings*, 1923, xvi, Sect.

[1] See illustration (fig 2) in *Proceedings*, 1929, xxii, 1551, Sect. Laryn., 62.

Laryng., 61) that the patient was treated by the ordinary technique employed for several years at King's College and the Cancer Hospitals, except that a larger dose at more frequent intervals was given. The radiation was the most penetrating which the hospital apparatus, a 16-in. coil, would yield, increasing up to a 10-in. spark, approximately 130,000 to 150,000 volts. The filtration was through 8 mm. of aluminium, and a pad on the skin provided a second filtration to prevent secondary radiations damaging the skin. Twice a week for a month the patient had a full dose of the rays directed on to his larynx, first from the left side, then from the right, followed for several months at fortnightly intervals. Altogether he had twenty hours of exposure, spread over a considerable time. A striking feature was that this frequent exposure had produced no effect on the skin.

In 1929 a man, aged 71, who had been treated by Dr. Coutard, came to consult him (the speaker) at the Cancer Hospital. In 1923 he developed progressive hoarseness followed by slight dyspnœa, without pain or difficulty in swallowing. In January 1924 he was seen by Dr. Hautant, of Paris, who reported: "Neoplastic ulceration, glottic and, especially, subglottic, but not extending beyond the lower border of the cricoid cartilage; the ulceration was not infected; the margins and base showed granulations; the anterior half of the left cord was fixed; the posterior third slightly mobile; the cartilage was probably involved in its anterior part; the

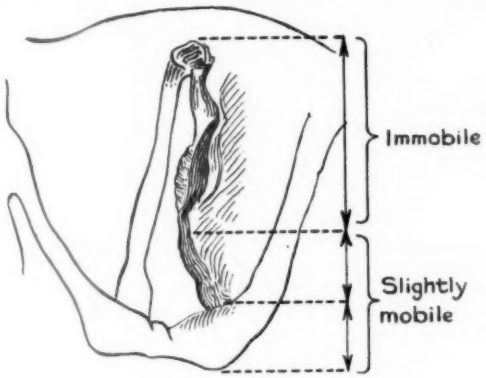


FIG. 1 (7.1.24)

ventricular band was infiltrated. Aphonia was complete. There was no glandular enlargement" (fig. 1).

The biopsy of a portion removed by Dr. Hautant for examination was reported as follows: "Small epithelioma in its early stage with non-differentiated cells, probably developed on an old inflammatory lesion. There was no mitosis; the structure was that of commencing 'basaliomes.' There was no stroma, the neighbouring connective tissue showing a thin lymphocytic barrier in which there were some mastocytes."

"Treatment by means of X-rays was then commenced by Dr. Coutard and was carried out in two series of exposures: the first for ten days, followed by a period of repose for twelve days; the second series was of six days' duration. The total length of treatment was twenty-eight days. The tension applied to the tube was 180,000 volts, the filtration 1 mm. of zinc and 3 mm. of aluminium: the distance of the lamp from the skin was 40 cm. The field of exposure measured about 40 sq. cm. The total duration of treatment was seventeen hours and the dose 78 Holtzknecht units, 50 on the left side and 28 on the right. Thirteen days from the

commencement of treatment there was noted diminution in the thickness of the ventricular band " (fig. 2).

On January 30, 1924, the left vocal cord was visible in all its extent, there being a longitudinal ulcer with two lips, one subglottic, the other subventricular. No further X-ray treatment was carried out. On February 14 there was a slight radio-epidermatitis of the skin, also radio-epithelitis of the pharynx and larynx at the level of both ventricular bands, with false membrane but no œdema. There was still some infiltration of the left ventricular band, but the voice began to return and the post-Roentgen dysphagia passed off. In March the voice became more and more

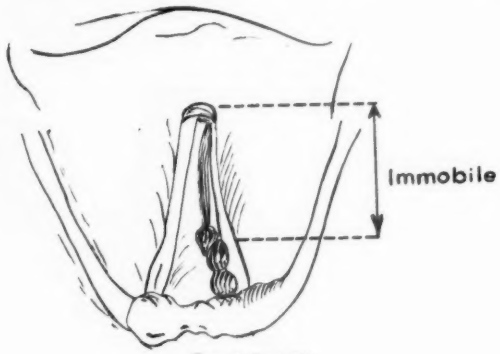


FIG. 2 (21.1.24)

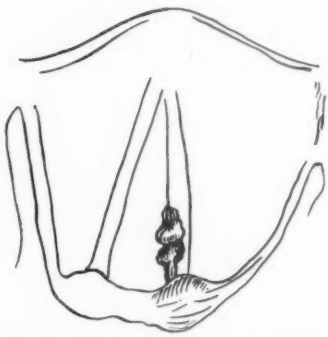


FIG. 3 (10.3.34). The vocal cord is visible. There remain three or four white, hard granulations which are contracting. The subglottic space is free.

clear, the left vocal cord more mobile and the granulations at the posterior part became flatter ; four days later the vocal cord was visible from the commissure to the arytenoid, there remaining three or four small very white granulations at the posterior part (fig. 3).

The subglottic space was quite free. The general condition became excellent. In December 1924 there were slight reactional phenomena, such as a sensation of dryness of the throat, perversion of taste, and slight subcutaneous œdema over the regions to which the rays had been applied. The patient came to the Cancer Hospital June 12, 1929, for an opinion as to his condition. There was slight irregularity in

the outlines of the left vocal cord, but the surface was quite smooth and there was no sign of ulceration (fig. 4). He (the speaker) thought it would be agreed that the condition then was one of simple fibrosis. The voice was nearly normal.

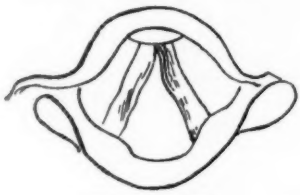


FIG. 4 (12.6.29)

He (Sir James) found it difficult to dissuade himself from the operation of laryngofissure in limited intrinsic epithelioma. Recently he heard from an old gentleman in the North from whose larynx he had removed an epithelioma twenty years ago. Therefore that treatment had obviously something to recommend it. He agreed, however, that when the irradiation method "came off," the results were incomparably good. For more extensive growths he was impressed by the results, even when only palliative, extending over a longer or shorter time, and by the immense comfort derived by the patients from X-ray and radium applications Epidermitis was an unpleasant complication, but, using irradiation in strengths which were effective for the cancer, such a complication was generally unavoidable and in time recoverable. He had been interested by what he had read in a paper by Mr. Sampson Handley, to the effect that dermatitis in the X-ray operator was a staphylococcal infection, that the rays diminished the immunity of the skin cells to the staphylococcus, and that benefit could be achieved by the application of staphylococcic anti-virus.

Fairchild's enzymol was said by Hayward Pinch to have a good clearing effect in some cases of epidermitis. He (the speaker) had found that the troublesome dryness of the mouth was considerably relieved by small doses of iodide of potassium and pellitory lozenges. He had been much gratified by to-night's discussion. As an old observer and operator it had been a great comfort to him to hear that there was hope of doing more for the distressing cases of extrinsic laryngeal cancer, which sometimes engendered feelings of despair. He hoped that in the future it would not be so often necessary to remove the whole larynx.

Dr. W. Levitt said that it was necessary to avoid confusion of the field arrangement with the time-intensity relation. One could make a protracted-fractionated irradiation using Finzi's field-method, one could make a fractionated irradiation by Dr. Webster's original method, as it had been shown on the screen, or one could carry it out by the Coutard method, which he (the speaker) regarded as inferior to the Finzi method as a field arrangement. The field arrangement adopted depended on whether the carcinoma of the larynx was approached as a localized growth, or as a growth with extensive glandular connexions and therefore extensive potentially infected masses of tissue all of which required to be irradiated. If the larynx was attacked as an isolated and localized structure, this was done by a series of small localized fields, and by a methed similar to that first shown by Dr. Webster; that method could be used as a protracted fractionated dose. But if it was desired, as he thought it should be, to attack the growth as one which had extensive glandular connexions, the method must be one which irradiated the greater portion of the neck except perhaps the posterior part, i.e. the vertebral column. For

that purpose he thought there was no means superior to the original Finzi method or its modifications.

With regard to the time and intensity factor, there could be no doubt that results had been improved since the treatment duration-time had been increased. When Dr. Finzi introduced his six-field method, the treatment was applied over a period of twelve days, and the dosage at the growth was about 220% over a fortnight. For some years, however, the tendency had been to increase the total duration of the treatment to as long as from four to six weeks, the dosage being correspondingly increased to 360%-400% of an erythema dose of 850 *r*, as compared with Coutard's 650 *r*, so that the final dosage, allowing for the difference of the original erythema dose, was very similar to that of Coutard. The latter being somewhat the higher accounted, the speaker thought, for the superiority in the results.

He did not think there was anything important in the question of *r* per minute. He thought Coutard must give two doses a day, because he was using a low *r* per minute. He, the speaker, had used enormous *r* per minute in his treatment of carcinoma of the œsophagus, and the primary results were better than those obtained by any other means.

Another point concerned the dose-time factor. It was extraordinary how well the results agreed with the time-relations published by himself in 1928, in which they estimated that 100% in one day, 150% over a week, and 280% over a month, were equivalent biological doses.

With regard to results, Dr. Webster had said he thought that the only method which had shown results at all in the same class as Coutard's was that of Holfelder. He (Mr. Levitt) thought that much depended on the classification of carcinoma of the larynx. He would like to know what diseases Coutard included in that category "carcinoma of the larynx"; did he include extensive pyriform fossa growths and post-cricoid growths? Or did he limit it to intrinsic and ventricular band growths? There was a considerable proportion of cases of the last two types, which were radio-sensitive, belonging to the lympho-epithelial type described by the Americans.

Mr. Cyril Horsford said that the patient in one of the cases quoted by Dr. Webster had come to him (the speaker) for another opinion as he had been advised to have total laryngectomy. He (Mr. Horsford) recognized that the patient was suffering from extensive intrinsic cancer, but, realizing the misery of patients who had had the total operation performed, felt sure that he could remove the whole disease by partial laryngectomy.

The patient willingly consented to the operation, which was carried out under local anæsthesia. Every trace of visible growth was removed with the cartilage adjacent in one mass. This he (Mr. Horsford) considered an advantage, in case the patient should in the future have any irradiation treatment. The patient did extremely well and left the nursing home a fortnight later.

Mr. Horsford then asked Dr. Webster to give a course of deep X-rays as a precautionary measure, and this was begun about six weeks after the operation.

This was a year ago and the patient was now well and spent much time riding a motor bicycle. He said he felt better than he had done for years.

He (Mr. Horsford) wondered whether the expected reaction to the rays was due to the presence of even microscopic portions of diseased tissue left behind. Would such reaction be likely if no island of cancerous tissue remained? Dr. Webster did not enter into the question of the reaction in the case just quoted. There had been no reaction in the interior of the larynx, though a tracheotomy tube had been put into the wound as a precaution; there was no more than a redness of the skin outside. Therefore the patient suffered no discomfort from the irradiation given, but

he, Mr. Horsford, felt it his duty to recommend that as a precaution. The cancer was so extensive that two laryngologists recommended total laryngectomy, and so it was essential that nothing should be left undone which would ensure complete recovery.

He (the speaker) was persuaded to try deep X-rays because eight years ago another patient, also a clergyman, was sent to him with a small growth on the vocal cord. This was removed and found to be malignant. He advised removal of the whole cord by thyrotomy, but the patient refused the operation and went to Guy's Hospital to have another opinion. Mr. W. M. Mollison did not discover any growth, but recommended deep X-ray treatment. This was carried out by Dr. Watt. The patient was now well, and without sign of recurrence. This was an excellent example of the advantages of deep X-ray therapy, especially as by indirect laryngoscopy one could not have expected to remove all the infiltrated tissue from the cord.

Dr. F. Hernaman-Johnson said he wished to ask Dr. Webster if he considered that all patients treated by the Coutard or similar method should be in hospital the whole time? or did he think it might ever be justifiable to treat any as out-patients?

Had he any experience of the effects of using lanoline on the skin of the operator during the exposure or before it? Did it modify the skin reaction?

Did Dr. Webster know anything of the method of treatment at the other extreme? He (the speaker) understood that a German worker had been concentrating an enormous dose in two or three minutes.

Mr. Harmer had laid stress on pre-operative treatment, and he (the speaker) thought that not only carcinoma of the larynx, but all malignant growths should be given reasonable X-ray exposure before operation, thereby reducing the activity of the cancer cells.

Dr. Webster (in reply) said he accepted Mr. Harmer's correction of the phrase in the synopsis. He hoped that a point made by Mr. Harmer would be taken to heart by some radiologists, namely, that only very high dosages were of use for laryngeal cancer. A number of his colleagues did not believe in high voltages or dosages for cancer, and Mr. Levitt had recently scarified them! The President of the Section and others had disparaged the use of high dosages.

He (the speaker) did not think that Dr. Finzi's doses were as high as these cancer cases needed. [Dr. Finzi: You are taking units as 600 *r*, ours is a 900 *r* unit.] Coutard began by giving his doses as measured by the Holzknecht method. By Borak it was discovered that Coutard was giving "1 H," which, measured in Vienna, was 3·5 H! The "*r*" unit was a much more accurate method.

Dr. Levitt thought that the Coutard field arrangement was not so good as the Finzi; he (the speaker) did not agree, because the Finzi method treated the whole posterior half of the neck, and that was unnecessary; the anterior hemisphere was all-important. Coutard recommended a number of different field-plans: more on the affected side, for unilateral lesions.

Mr. Horsford had said that the patient whom they had both treated showed very little skin reaction. This was because he (the speaker) had divided the dose equally on both sides. Some of Coutard's cases were unilateral, with a mass of glands: in such cases there was a marked one-sided skin reaction.

Hünermann, of Düsseldorf, treated eight patients having cancer of the larynx; he could not try the Coutard method, but he used a fractional method, giving equivalent doses. Five of the eight patients became symptom-free of growths in the larynx, but in every case the growth recurred in six months, and the patients died. At a discussion held by the Laryngological Society in Bad Ems, Holthusen said that

Hünermann had not given a large enough dose, but what he gave apparently was 700% in nine days.

Stewart-Harrison had told him (Dr. Webster) that cases of œsophagus cancer treated in Zurich by the simple fractional method did very well, but only for six months, death then following from lung induration. Experimental work by Zwerg and others had shown that the protraction of each dose had less permanent effect on the skin, the vessels, the lungs, the kidneys and the blood, and if that were so, clearly it was the method to adopt.

Section of Surgery

SUB-SECTION OF PROCTOLOGY

President—W. Ernest Miles, F.R.C.S.

[*March* 14, 1934]

Adeno-carcinoma of Anal Skin.—J. P. Lockhart-Mummery, F.R.C.S.

C. R., male, aged 58, came to the out-patient department of St. Mark's Hospital complaining of soreness and discomfort at the anus, with slight swelling and discharge. This had been going on for about two months.

On examination.—There was a small hard ulcer on the left anterior aspect of the anus; the edges were indurated and the ulcer extended up almost, but not quite, to the margin of the anus. The floor showed sloughy granulation, and the whole appearance was typical of epithelioma. There were hard, mobile glands in both groins. Nothing abnormal was felt or seen in the rectum.

In November 1933 the patient was treated by radium insertion.

Two months later the ulcer had healed up entirely, but there was still some induration on the edge, towards the anterior part of the anus. When seen on March 1, 1934, it was evident that the condition was recurring and it had not entirely been got rid of by the initial treatment.

Pathological report.—A portion of the ulcer removed at the first operation proved to be a columnar-celled adeno-carcinoma growing in and beneath the skin. It is clear that this tumour has arisen in the mucous cells situated outside the anal margin, and in the cutaneous area.

From a clinical standpoint, its behaviour is like that of an epithelioma and it tends to invade the lymphatic areas in the inguinal glands. The question arises whether it should have been treated by complete excision of the rectum and clearing of the gland areas. In view of its situation, and the fact that epithelioma of the anal margin reacts extremely well to radium, it was decided to treat it by radium.

Fibroma of the Ovary—presenting in the Rectum.—J. P. Lockhart-Mummery, F.R.C.S.

Miss L., aged 22. The patient appeared to be quite a healthy girl, who had consulted her doctor because she had not menstruated for a year, and had only menstruated on two occasions during her life, although each month she had all the usual sensations, without any loss.

On rectal examination.—A number of hard nodular masses were easily felt, obviously not in the rectum but projecting into it from Douglas's pouch. There were four or five separate hard fibrous lumps, the largest bigger than a walnut. They were not tender and apparently lay somewhere in Douglas's pouch and pushed

through the anterior rectal wall into the rectal lumen. Examination per vaginam appeared to show that they were not connected with the uterus. The total size of the mass was very considerable and almost obstructed the rectum. There was no tenderness or pain and the mass was freely mobile.

It was decided to explore the abdomen, and the tumours were then found to be ovarian in origin. The largest one was about as large as a man's fist, and looked like a cauliflower. The other was about a quarter this size and was in the opposite ovary. There were no "chocolate" cysts and no growths anywhere in the pelvis or other parts of the abdomen, or in the liver.

The ovaries were both removed, as there was no possibility of removing the tumours otherwise, and no evidence of any normal ovarian tissue.

Pathological examination showed the growth to be a fibroma.

Adeno-carcinoma of the Abdominal Wall.—J. P. LOCKHART-MUMMERY, F.R.C.S.

J. W., male, aged 54, had a gangrenous appendix removed in February 1931. The operation was followed by a fæcal fistula which refused to heal, though it was curetted in September 1931. I saw the patient in January 1932, about a year after the original operation. He then had a large tumour, consisting of an adeno-carcinoma, growing at the site of the original sinus on the abdominal wall. I removed part of the abdominal wall, the whole cæcum, the ascending colon and glands, and joined the ileum into the transverse colon. I also inserted a number of radon seeds.

The patient made a good recovery and remained in good health till September 1933. He then developed secondary growths in the lungs and died a few months later.

The specimen shows an adeno-carcinoma of the cæcal wall spreading out on to the skin along the site of the drainage tube. This had probably been the cause of the appendix becoming gangrenous.

Lymphoma of the Rectum: with Report of Three Cases.

By CUTHBERT DUKES, M.D.

IN each of these cases the growth was considered, from its gross characters, to be an adenoma, but microscopic examination showed it to consist only of lymphoid tissue. In each case also there was some difficulty in deciding whether the tumour was a lymphoma or a lymphosarcoma, but it is now five years since the operation on two of the patients, and there has been no sign of recurrence.

Tumours composed of lymphoid tissue arise from the lymphoid follicles which lie in the submucosa. These are present throughout the colon to the extent of about three per square centimetre of surface area and are a little more numerous in the rectum.[1] Their function is to produce lymphocytes and also to filter the lymph which is collected from the lymphatic vessels of the mucous membrane.

When lymphoid tissue is increased in quantity it is often difficult to decide whether the condition is an inflammatory hyperplasia or a genuine new growth. In chronic lymphadenitis there may appear to be an actual multiplication of follicles in the lymphatic tissue, but the glandular enlargement is more diffuse and the histology more regular than is seen in lymphoma. In the three cases about to be described the new growth seemed more like a tumour than an inflammatory hyperplasia, because of its large size, its isolated character and definite boundaries.

1 Dukes and Bussey, *Journ. of Path. and Bact.*, 1926, xxix, 111

The first case is that of a man, aged 38, who was admitted to St. Mark's Hospital with a complaint of bleeding and slight prolapse for four years. Examination showed a pedunculated tumour $\frac{3}{4}$ in. in diameter, resembling an adenoma. Mr. E. T. C. Milligan removed it by excision and ligature. Microscopic examination showed the tissue to consist of a closely packed mass of lymphoid follicles lying in the submucosa and covered by normal mucous membrane. A blood-count was carried out in order to exclude lymphatic leukæmia and a Wassermann test in order to exclude syphilis. No other enlargements of lymphatic tissues were found. There was no evidence or history of tuberculosis. In the five years which have elapsed since the tumour was removed there has been no recurrence, and the patient is now in good health.

The second case is that of a man, aged 32, who was admitted to St. Mark's Hospital complaining of prolapse and bleeding for two years. A large pedunculated tumour, described as being of the size of a pigeon's egg, was found in the lower third of the rectum. This was removed by Mr. W. B. Gabriel in 1929. This tumour also was composed only of lymphoid tissue. The Wassermann reaction was negative, the blood-count was normal, and there was no other enlargement of lymphoid tissue. The patient has remained in good health for the last five years.

The third patient is a woman, aged 59, admitted to St. Mark's Hospital in January 1934, and found to have a curious submucous induration about half an inch in diameter in the left lateral wall of the rectum. The tumour was removed by Mr. Gabriel and found to be a lymphoma. The tumour has the same histological structure as the other two cases.

I have not been able to find any mention of lymphoma of the rectum in any textbook of proctology, ancient or modern, except Sir Charles Ball's "Diseases of the Rectum" (1908), and Mr. W. B. Gabriel's "Principles and Practice of Rectal Surgery" (1932). Sir Charles Ball says that in his case (that of a boy aged 6) "the general character resembled that of ordinary adenomata, but, upon minute examination, these were found to consist almost entirely of lymphoid tissue." And he continues: "A few similar cases are met with in literature; possibly many have been overlooked, being mistaken for simple adenomata, to which they bear a close resemblance" (p. 230). The case referred to in Mr. Gabriel's book (p. 157) is the second of those which I have now reported.

Although these tumours are rare they certainly deserve to be mentioned particularly, because the histology so closely resembles that of lymphosarcoma, a condition which, of course, requires quite different surgical treatment.

Rectal Prolapse treated by Amputation.—W. B. GABRIEL, M.S.

Mrs. A. M., a very stout subject, aged 56, had a large circular prolapse of the rectum. The prolapse had existed for many years and came down on walking or at the least exertion. There was incontinence of urine and fæces. The external sphincter was greatly stretched and showed no contractile power. Amputation of the prolapsing bowel was effected on January 25, 1934, under spinal anæsthesia. The usual great disproportion in size between the outer and inner layers was overcome by placing four mattress sutures N. S. E. and W. between them, and then distributing the excess of the outer circumference evenly in each quadrant.

The specimen [exhibited] measures 9 in. in length and shows clearly the narrow pelvic colon at the upper end of the specimen compared with the bulbous and thickened rectal end of the prolapse. The patient made a good recovery. On her discharge home four weeks after operation she had good bowel control and showed improving tone in the sphincter and levatores ani. The sphincter is now (March 1934) easily palpable to a finger; there is no stricture at the suture-line and the bowels are open regularly.

Anal Lipoma.—W. B. GABRIEL, M.S.

Miss L. H., aged 35, complained of a swelling near the anus, of three years' duration. Examination showed a soft oval mass $2\frac{1}{2}$ in. by $1\frac{1}{2}$ in. in the left posterior

anal quadrant; the overlying skin was pale, there was no induration or tenderness, and a small outlying nodule indicated the diagnosis of a lipoma. The tumour was removed by operation in November 1933.

Carcinoma of the Pelvic Colon.—W. B. GABRIEL, M.S.

The specimen [shown] is a portion of the pelvic colon 8 in. in length, with a fungating carcinoma which extends completely round the bowel for 2 in. The excised portion of the pelvic mesocolon contains a number of enlarged glands which have been dissected out; microscopical examination has proved metastases to be present in four out of the 13 glands examined. The prognosis is clearly bad, but the two facts which give some slight hope for eventual cure are: (1) That there were no palpably enlarged glands other than the ones removed, and (2) that the glands nearest the ligated edge of the mesocolon are free from growth, as judged with the microscope. This specimen was obtained in November 1933, by Paul's operation, from a man aged 59; I applied a Dupuytren's enterotome to the colostomy spur on the third day and carried out the final extraperitoneal closure of the fæcal fistula six weeks after the primary operation. The wound healed without fæcal leakage and the patient is now abroad convalescent.

Colloid Carcinoma of Cæcum with Chronic Intussusception producing Severe Anæmia treated by Resection and Anastomosis after Blood Transfusions.—Sir CHARLES GORDON-WATSON, K.B.E., F.R.C.S.

The patient, a man aged 59, who had had anæmia with occult blood in stools for two years, was suspected to be suffering from duodenal ulcer.

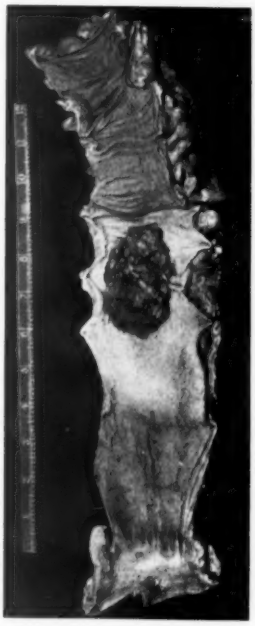
When his blood was examined three weeks before operation, the hæmoglobin was down to 46%. This was raised to 86% by three blood transfusions and iron treatment before operation. Recovery after operation was uneventful.

Two Cases of Recto-sigmoidal Carcinoma treated by Two-stage Perineo-abdominal Excision.—LIONEL E. C. NORBURY, F.R.C.S.

The interest of these cases lies in the fact that the patients were both bad operation risks on account of their general condition and poor renal function, as shown by the "urea clearance test" (Dr. Cuthbert Dukes). They were both "A" cases, and the renal function markedly improved after operation.

I.—S. S., female, aged 62. Symptoms of diarrhœa and hæmorrhage, one year; loss of weight. Growth felt and seen at recto-sigmoidal junction.

September 9, 1933: Exploratory laparotomy. Growth felt at peritoneal reflection. No evidence of metastases.



Carcinoma recti. (Case S.S.)

Operation.—(1) Left iliac colostomy, with closure of lateral space. Further operation postponed until October 13, on account of poor renal function. General condition improved, and it was decided to take risk. (2) Perineo-abdominal excision. Many abdominal adhesions, partly due to appendicectomy three years previously. Small gut adherent to abdominal scar, and portion accidentally injured, necessitating suture.

Good recovery. Progressive improvement in renal function occurred. Urea clearance previous to operation was 32% of normal but ten days after operation was 61% of normal. No urinary infection followed operation.

The specimen measures 17 in., and shows an oval fungating growth, 3 in. in its long axis and extending half-way round the bowel, in the region of recto-sigmoidal junction.

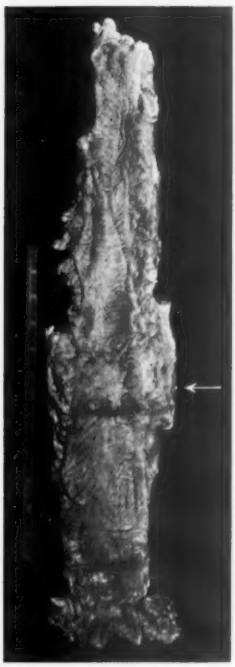
Microscopical examination showed the tumour to be an adeno-carcinoma, which had infiltrated the muscular coats. No glandular metastases.

II.—Mrs. K., aged 56. History of six weeks' diarrhœa and hæmorrhage. Growth present in recto-sigmoidal region.

July 11, 1933. Laparotomy and colostomy, with closure of lateral space. No metastases visible. Left femoral thrombosis followed, and so further operation had to be postponed.

Kidney function was bad, but general condition improved.

November 25, 1933 (i.e. four and a half months after colostomy), perineo-abdominal excision of the rectum. Considerable post-operation shock. Blood transfusion on following day. Good recovery.



Carcinoma recti. (Mrs. K.)

Urea clearance.—Before operation = 24% of normal; after operation = 41% of normal.

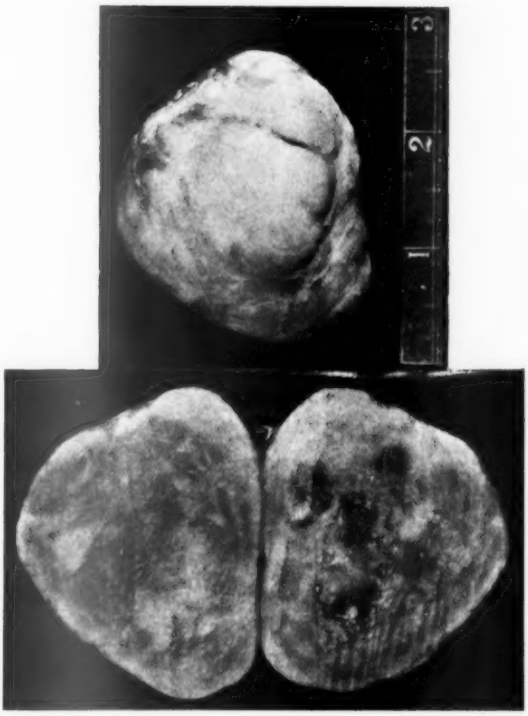
The specimen measures 24 in. Ulcerating growth 2½ in. in diameter, extended completely round the upper fifth of the rectum. Several small papillomata present.

Microscopical examination.—Adeno-carcinoma, which had involved the circular —but not the longitudinal muscle coat. No metastases in glands.

Specimen of Post-rectal Fibro-leiomyoma.—LIONEL NORBURY, F.R.C.S.

R. K., male, aged 32. *History*: Prolapsing pile on defæcation. Examined by doctor, who discovered a tumour projecting into the rectum posteriorly.

On digital examination.—Smooth rounded swelling, size of tangerine orange, felt through posterior rectal wall, apparently fixed to the sacrum. The mucous membrane over this was normal.



Post-rectal fibro-leiomyoma.

Sigmoidoscopy.—Negative.

Diagnosis.—(?) Sarcoma. (?) Fibroma. (?) Notochordoma.

X-ray examination showed no erosion of the sacrum.

Operation (October 16, 1933). Excision of coccyx and portion of sacrum. Hard encapsuled tumour removed from posterior wall of rectum.

The specimen consists of an oval mass 2½ in. by 2 in. Outer surface smooth and slightly lobulated. The tumour appeared to be completely surrounded by a capsule.

Microscopical examination showed the tumour to be composed of interlacing strands of fibrous tissue and unstriped muscle, and therefore to be a fibro-leiomyoma. No sign of malignancy.

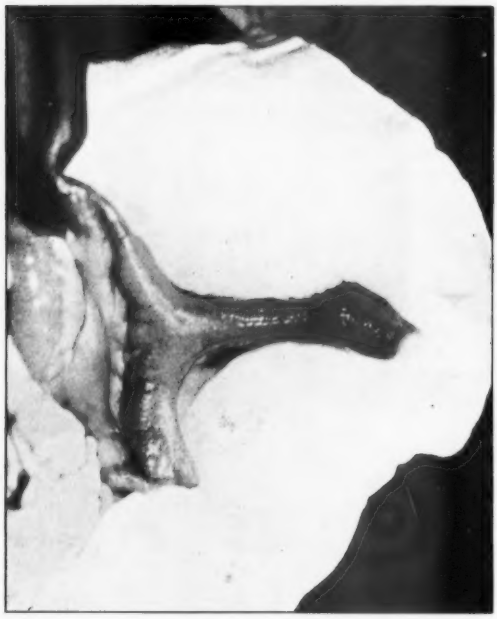
Inflamed Meckel's Diverticulum felt per Rectum.—LIONEL NORBURY, F.R.C.S.

Male, aged 57 years.

History.—Three weeks previously had an attack of colic in lower abdomen and back. Occasional diarrhœa; some bleeding per rectum. Indigestion for some years; said to have had piles for five or six years.

Examination per rectum.—Mass felt through rectal wall; high up; not tender.

Sigmoidoscopy.—Negative.



Meckel's diverticulum.

Barium enema and X-ray examination.—Nothing abnormal except a "spastic and irritable condition of the colon, probably due to a recent inflammatory state of the parts."

Abdominal exploration, February 20, 1934.—Inflamed Meckel's diverticulum, arising from the ileum, about 15 in. from the cæcum. Much stretched and elongated (about 6 in. in length). Distal end firmly adherent to pouch of Douglas, rectum and bladder. Diverticulum freed with much difficulty. Appendix also removed. Drainage of pelvic cavity.

The diverticulum had a well-formed mesentery continuous with that of the small gut. A large abscess cavity was present at the distal end, and there were several smaller abscesses in the wall of the proximal portion.

The patient died four days later from "paralytic ileus," in spite of the fact that the bowels had been opened slightly and flatus passed on the third day.

Fistula-in-ano, caused by the Ova of Oxyuris vermicularis.—DUNCAN C. L. FITZWILLIAMS, C.M.G., F.R.C.S.

A. P., male, aged 17. Admitted, 5.2.33 to St. Mary's Hospital, complaining of tenderness of the rectum. There had been an abscess near the anus, and there was a discharge of pus now and then, though none could be made out on examination. The tenderness was first noticed in May 1932, when an abscess formed : following the application of hot fomentation a watery blood-stained pus was discharged. In July and again in December an abscess formed at the same place and another appeared early in January 1934.

At operation, February 5, 1934, the diseased tissue was removed. There was no external opening, but on incising and cutting away the tissue with scissors, several small pockets of pus were discovered. No definite fistulous passages were found,

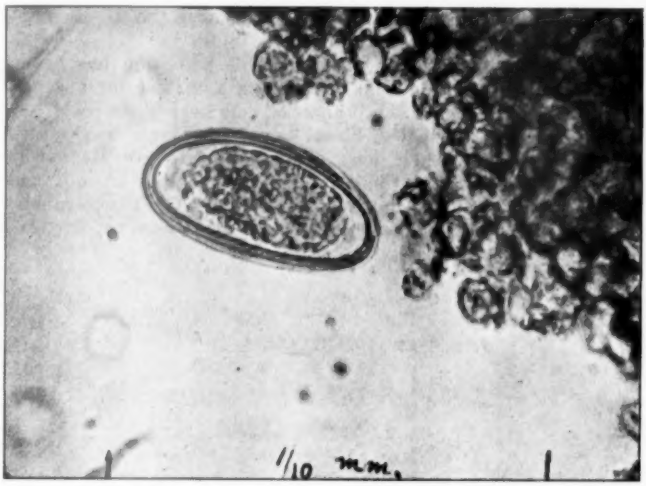


FIG. 1.—*Oxyuris vermicularis* egg from pus.

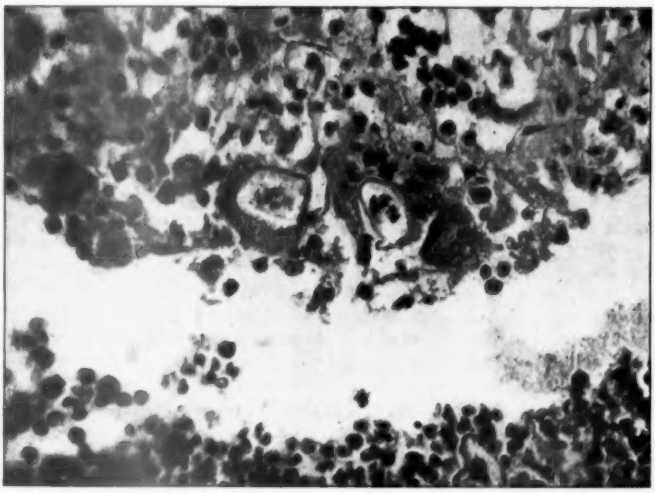


FIG. 2.—High power view of eggs in giant cells.

and therefore the tissue was removed very freely. The condition was puzzling at the time, and the tissue was sent to the pathological department. The report stated that large numbers of eggs were found in the tissue; these were first thought to be

bilharzia, but the patient had never been abroad, and further examination proved that they were the eggs of threadworms (figs. 1 and 2). The stools were examined and large numbers of worms were found. It now transpired that the patient had had threadworms ever since childhood. He was given rectal wash-outs of quassia. Three weeks later there were no signs of eggs or worms in the stools. The wound has been healing slowly.

Conclusion.—I know of no case in which this condition has been previously described. How the eggs got in that position is a matter for speculation, but I imagine that, before the ischiorectal abscess had healed properly, one or more worms must have escaped from the bowel and found their way into the abscess cavity, and there deposited their eggs. These worms are frequently found in appendix abscesses and may make their way through healthy mucous membrane into the submucosa of the gut. Superficial peri-anal tumours due to enterobius infestation have been described, but I do not think that any have been reported in the ischiorectal fossa.

Section for the Study of Disease in Children

President—F. C. PYBUS, M.S.

[*February* 23, 1934]

The Union of Fractures of Long Bones in Newborn Infants, without Surgical Treatment

By ERIC PRITCHARD, M.D., F.R.C.P. and JEAN SMITH, M.D., M.R.C.P.

FRACTURES of bone, and more especially fractures of long bones, in newborn infants are generally treated on the orthodox surgical principles of securing immobility and maintaining good position of the fragments by means of bandages, strapping, splinting, or extension apparatus. The object of this paper is to suggest that all such surgical expedients are quite unnecessary, and make good nursing extremely difficult. Further, perfect union can take place if the case is left severely alone and treated merely on sound hygienic principles.

Some little time ago we had at the Infants Hospital a case of extreme fragility of bone in a young infant in whom there were more than a dozen fractures, involving the limbs and ribs. The fractures in this case were too numerous to be treated by the surgical means of splinting, so the baby was left to its own devices and allowed entire liberty of movement. Adequate doses of vitamin D and calcium salts were given, however, in order to promote ossification. Recovery took place in a surprisingly rapid manner, and at the age of eighteen months—that is to say sixteen months after its first admission to the hospital—no trace of the original fractures could be discovered clinically, or by means of X-rays. This experience, combined with certain others of a somewhat similar nature which also showed rapid osteogenesis in young infants under appropriate medical treatment, encouraged us to apply the same line of treatment in the relatively simple case of obstetric fractures in newborn babies, with results which are here recorded.

The capacity of completely undifferentiated pieces of cartilage taken from embryo chicks to develop into perfectly shaped bones under suitable nutritive conditions *in vitro* has been explained by Honor Bridget Fell [1] in communications to the *Biochemical Journal*, and more recently demonstrated in a very beautiful micro-photographic film, in which were shown all the stages of growth in an embryonic femur completely separated from its vascular, nervous, and muscular connexions. The striking capacity of rudimentary bones in early embryonic stages to exfoliate

along normal lines into fully developed and normally shaped bones in response to some as yet unexplained urge of their own self-differentiating tendencies is exemplified, though to a less degree, in our own cases, which seem to show that there is indeed some "Divinity which shapes" the ends of fractured bones in newborn infants "rough-hew them as we will."

Although in the literature on the subject of the treatment of fractured bones in the newborn there are occasional references (Pearce [2], Ehrenfest [3]) to the ease and rapidity with which such fractures unite without obvious deformity nevertheless, in writings on orthopædic surgery and midwifery the usual methods of treatment advocated almost invariably involve the use of either Thomas's, the Gallows, of plaster of Paris splints. One French writer goes so far as to maintain that the best method of treatment for obstetric fractures is to reduce the deformity under a general anæsthetic, and apply a plaster of Paris splint, the cumbrous nature of which is perhaps best described in his own words: "Un grand appareil plâtré prenant le bassin, tout le membre fracturé et les deux tiers de la cuisse du côté sain." He further added that—"Depuis l'application de cette méthode mes résultats sont constants et tellement parfaits que je n'ai plus éprouvé la moindre envie d'en changer."

Even those who realize that perfect anatomical reduction is not essential for complete functional recovery still adhere to the time-honoured surgical methods, and most of them advocate such complicated apparatus that retention in hospital with all its attendant evils is rendered necessary. It is impossible to emphasize too strongly that the restraint imposed on the infant by apparatus of this kind, which restricts liberty of movement, inevitably leads to nervous irritability and possibly to secondary nutritional disturbances.

The first of the following cases shows the excellent result obtained, although no surgical treatment of any kind was adopted.

Case I.—This child was born on February 1, 1932, at Queen Charlotte s Hospital; there had been an extended breech presentation with a fracture in the middle of the shaft of the femur. When the child was three days old the fracture was put up in the usual fœtal position, and fixed with bandages, with the thigh flexed on the abdomen. The infant was extremely uncomfortable and restless, and nursing was almost impossible. All bandages were therefore removed and directions given for the child to attend at the Infants Hospital as soon as the mother was able to bring it.

The first photograph (fig. 1) was taken when the child was 11 days old. It shows considerable over-riding, but not very much angular displacement, in fact not nearly so much as is seen in the two following cases.

The second photograph (fig. 2) was taken when the infant was three weeks old, and shows an enormous amount of provisional callus, definitely more than in either of the next two cases, but with the two fragments lying practically parallel. The exudate may have been encouraged by the liberty of movement, and its density by the administration of vitamin D and calcium salts.

Figure 3 taken a month later (March 18, 1932), shows a well-marked bridge of bone forming in the provisional callus. The axis of the bone appears to be straightening out in a very promising manner. It will be noticed in this photograph that the new bridge of bone is not growing from the extremities of the two fragments, but from the sides of the shafts, indicating one manner in which Nature preserves the intended design of a bone, and makes provision for growth and compensatory lengthening.

Figure 4, taken fourteen days later—when the child was 2½ months old—shows further modelling of the new shaft and improved alignment.

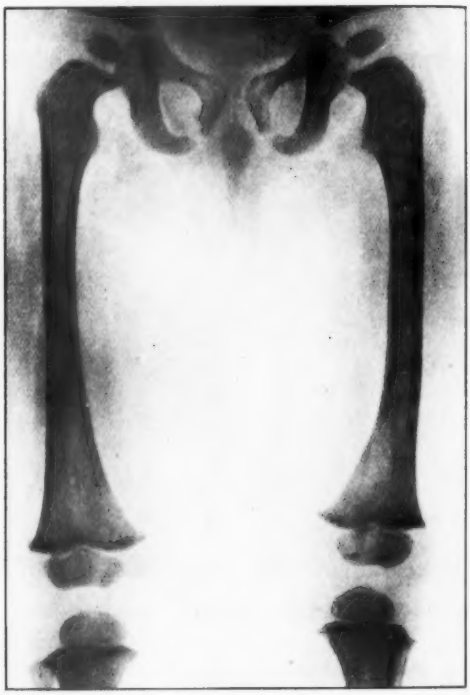
Case I. Fig. 1.

Case I. Fig. 2.

Case I. Fig. 3.

Case I. Fig. 4.

Case I. Fig. 5.



Case I. Fig. 6.

Figure 5, taken at the age of 5¼ months, shows that by that time the bone had resumed its normal shape. Clinically, there was no shortening.

Figure 6 was taken when the child was 10 months old. The site of the fracture is scarcely discernible. The child is walking normally.

The next two cases illustrate the manner in which Nature retrieves surgical failure and achieves her predestined ends in spite of human interference.

(The series of photographs demonstrating the progress of these cases, though shown at the meeting, are omitted from this report owing to lack of space.)

Case II.—This infant was born on December 1, 1932. It was a breech presentation and during the process of bringing down the legs the right femur was fractured in the upper third. This was reduced and put up in a side splint under X-ray (screen) illumination. A fortnight later the fragments as shown by X-rays were still in a very bad position, and after ineffectual attempts to correct this by splinting the case was admitted to the Infants Hospital for treatment.

A photograph taken after thirteen days splinting and before the infant was referred to the Infants Hospital, showed marked displacement of the fragments. Little callus had been thrown out, and the condition was unpromising.

In the Infants Hospital no splinting or other form of apparatus was applied, but osteogenesis was encouraged by the administration of vitamin D and calcium lactate. A photograph taken when the infant was seven weeks old (thirteen days after admission to the hospital) showed an immense amount of dense callus, and a slight tendency for straightening out of the long axis of the bone.

X-ray photographs taken at frequent intervals during the first year showed gradual resumption of the normal alignment of the bone. Moreover, the child's activity was in no way retarded. He crawled rapidly at ten months, and was walking well alone at the end of the first year.

Case III.—This was a full-time infant, weighing 9 lb. Breech presentation; fracture occurred in bringing down the legs. This case strikingly illustrates the triumph of Nature over ineffectual surgical treatment and splinting.

A photograph taken one day after birth showed a fracture of the upper third with considerable displacement and overlapping.

The thigh was put up in a plaster-of-Paris splint, which was removed the following day as X-ray examination showed no improvement in the position of the fragments. The thigh was then strapped up with the leg fixed in the usual fœtal position with the leg flexed on the abdomen, but a photograph taken when the child was 14 days old showed the still unchanged position of the fragments, with a considerable amount of provisional callus between the fragments, and also some round the ends of the bones. From that time onwards all artificial attempts to keep the fragments in position were omitted.

At three months, however, there was firm union and less deformity, with considerable straightening out of the axis of the bone, and at 10½ months the femur was scarcely distinguishable from its fellow on the other side, with no external deformity, limitation of movement, or shortening.

When the child was 18 months old no difference could be observed clinically between the two legs, and the child was walking about well and actively.

[NOTE.—A cinematograph film of Case II was shown, in which the child, aged 1 year, was seen walking about actively without any limp.]

REFERENCES

1 FELL, H. B., *Biochem. Journ.*, 1929, xxiii, 767-784.
2 PEARCE, N. O., Abt's "Pediatrics," ii, 377.
3 EHRENFEST, H., "Birth Injuries in the Child," 2nd Ed., 1931, 300.

The PRESIDENT said that Nature had been healing fractures since before the appearance of man on this planet, and it was well known that repair at this early age was most efficient. The film illustrated very well the repair and functional result which could be obtained without restraining apparatus. He felt certain, however, that a better result could be achieved by suitable reduction of the fracture and its immobilization by some retentive apparatus. It was generally found that if any apparatus were comfortable, even in early infancy the patients remained perfectly happy, and one could at least avoid the possibility of any shortening—which was certainly present in some of the illustrations shown.

Cirrhosis of the Liver and Splenomegaly in Three Brothers.—FREDERICK LANGMEAD, M.D.

Family history.—The mother has been married twice. In the first family are two males and three females, none of whom appear to be affected. In the second family, after a miscarriage, there are five children; the eldest, a boy aged 16, and a boy aged 12 are unaffected. The remaining three are shown this afternoon. They are aged 13, 11, and 9, all boys. Consanguinity between the parents is denied.

The date of onset is uncertain in each case. The eldest boy came under observation in hospital on August 1, 1933, being admitted on account of hæmatemesis. He had had a similar attack four or five years previously. A history was then obtained from the mother that the two other children were supposed to be suffering from the same disease. In the case of the second boy there is a history of bringing up blood just before last Christmas, 1933. Apart from the hæmatemesis in these two cases there is no history of any symptoms which might be ascribed to

the cirrhosis. They appear to have been in good health and to have taken an active part in games at school.

Condition on examination.—There is a striking similarity in the three cases. In all there is considerable enlargement of the liver, which is definitely harder than normal, has a sharp edge which can easily be picked up between two fingers, and a surface which appears to be finely nodular. In each case the enlargement of the liver is chiefly of the physiological left lobe. In the case of the second boy the enlargement is confined to that lobe. It is probable, however, that the right lobe is similarly affected, since the hepatic dullness is diminished and ends at the level of the 6th rib in the mid-clavicular line in the two younger boys. In all, the spleens are considerably enlarged, the enlargement being greatest in the case of the second boy—where it reaches nearly to the umbilicus—and least in the youngest boy. There are no unusual characteristics about the splenic enlargement in any of the cases. There is no history of jaundice, nor is jaundice present in any of them, and no other abnormal features of note have been found. There is a definite family resemblance between the three children and they are somewhat undersized.

The Wassermann reaction is negative in all three cases.

Blood-counts. (Mr. W. H. Hughes.)

Case I. Boy aged 13.

August 1933. *Hæmatemesis.*

R.B.C., 1,900,000 per c.mm.
Hb., 26%
C.I., 0·7
W.B.C., 3,600 per c.mm.

Differential count :—	%
Polymorphonuclears	76
Lymphocytes ...	12
Hyalines	8
Basophils	2
Eosinophils	2

Now (*February* 13, 1934), the blood-count is as follows :—

R.B.C., 4,450,000 per c.mm.
Hb., 74%
C.I., 0·85%
W.B.C., 7,000 per c.mm.

Differential count :—	%
Polymorphonuclears	72
Lymphocytes ...	17
Hyalines	5
Basophils	1
Eosinophils	5

Case II. Boy aged 11.

February 2, 1934.

R.B.C., 5,400,000 per c.mm.
Hb., 80%
C.I., 0·75
W.B.C., 7,000 per c.mm.

Differential count :—	%
Polymorphonuclears	72
Lymphocytes ...	15
Hyalines	11
Eosinophils	2

Case III. Boy aged 9.

February 7, 1934.

R.B.C., 4,900,000 per c.mm.
Hb., 62%
C.I., 0·7
W.B.C., 7,000 per c.mm.

Differential count :—	%
Polymorphonuclears	64
Lymphocytes ...	12
Hyalines	11
Eosinophils	12
Basophils	1

Fragility test in each case, normal. Size of R.B.C. in each case, approximately 7·1 μ; van den Bergh reaction, direct and indirect, negative in the two younger boys. Icteric index normal in the two younger boys. Lævulose tolerance test normal in the two younger children. (The three latter tests were not carried out in the older child.) The urine was normal in all and did not contain urobilin or bile-pigments. The normal value of the liver tests is probably explained by the high degree of regeneration present, which is probably also the explanation of the granular surface in each case.

The eldest boy has been under the care of my colleague, Sir William Willcox, to whom I am indebted for permission to include his case.

Comment.—The association of splenomegaly with cirrhosis of the liver in children is not very uncommon. When splenomegaly and anæmia are believed to have preceded cirrhosis of the multilobular form, there is little hesitation, in cases other

than syphilitic, in diagnosing splenic anæmia. When, on the other hand, the cirrhosis is advanced but there is little or no anæmia, primary cirrhosis of the liver is the usual diagnosis. On these grounds I have called these cases of hepatic cirrhosis, which I believe to be of the ordinary multilobular (so-called alcoholic) type. But when multilobular cirrhosis and considerable splenomegaly are met with together, I have little belief that the enlarged spleen is secondary to the cirrhosis. They are, in my opinion, either due to a common cause, or the spleen is initially the offending organ. This bears upon the question of splenectomy, and I have advised operation in cases in which cirrhosis appeared to be a more appropriate diagnosis than splenic anæmia, and in which it was seen to be present at the operation, yet the results have been very satisfactory. This contention is supported by the experience of the Mayo Clinic, where splenectomy has been employed for cirrhosis of the liver, and where the opinion has been formed that cirrhosis secondary to the splenomegaly is more usual than is generally supposed. Serious impairment of liver function, as tested by the lævulose or galactose test is, of course, a bar to operation.

Familial multilobular cirrhosis of the liver would appear to be rare, although it is well known to occur in splenic anæmia. I have had under my care two sisters with this disease, one of whom died from cholæmia, while the other, treated by splenectomy, made a good recovery. Ernest Jones,[1] in his symposium of cases of hepatic cirrhosis in children, does not mention cases of familial incidence. A family resembling that shown to-day was recorded by Byrom Bramwell[2] in 1910. The patient under his care, a boy aged 9, had ascites, œdema, jaundice, fever, and a large liver, and, post mortem, was found to have had typical "hob-nailed" cirrhosis. Three other members, girls, of a family of seven, apparently died from the same disease.

Szanto,[3] too, described three cases of multilobular cirrhosis of unknown origin, with splenomegaly, in a family of ten. One, a boy, aged 15, was examined post mortem. Genital hypoplasia was also present.

Discussion.—Dr. E. A. COCKAYNE said that Dr. Poynton had shown three children of the same fraternity with cirrhosis of the liver at the International Congress of Pædiatrics last year and he (the speaker) believed that they had previously been shown at a meeting of this Section. He feared that Professor Langmead took too optimistic a view of the value of splenectomy in preventing hæmatemesis. He (Dr. Cockayne) had known it occur in three patients after operation, and a little boy under his care had died last year from a second hæmatemesis after splenectomy performed more than a year before.

Dr. PARKES WEBER agreed that these cases were excellent examples of familial hepatic cirrhosis. On looking up his notes and references on the subject he found that quite a number of accounts of familial cases had already been published; the most interesting examples were those in which hepatic cirrhosis was associated with chronic lenticular degeneration (Kinnier Wilson's disease) in more than one member of the same family.

In all such familial cases there must be an inborn constitutional defect in the hepatic glandular cells, which diminished their powers of resistance towards toxins or caused them to decay prematurely, like the nucleus lenticularis in Kinnier Wilson's disease.

Dr. Weber thought that splenectomy was not advisable in Professor Langmead's cases, as splenectomy did not, it seemed, protect the patient from subsequent attacks of hæmatemesis, at least in ordinary types of hepatic cirrhosis.

Dr. Weber did not think that asymmetry in involvement of the liver could be used as an argument against the developmental explanation that he advocated. Many developmental anomalies in other parts of the body were asymmetrical.

Subsequent note (30.4.34).—Splenectomy was performed in Case II by Professor Pannett, 15.3.34, and at the same time a wedge of liver was excised for histological examination.

[1] Ernest Jones, *Brit. Journ. Child. Dis.*, 1907, iv, 1.
[2] Byrom Bramwell, *Clinical Studies*, 1910, viii, 347.
[3] Josef Szanto, *Monats. für Kinderheil.*, 1927, xxxvi, 393.

Pathological report (Dr. W. D. Newcomb).

Enlarged spleen weighing 400 grm. and measuring 15 × 10 × 4 cm. Greyish pink colour. Flabby but tough. Surface slightly roughened. Veins in hilum enlarged; on section, blood poured from it. Cut surface flat, Malpighian bodies standing up as pale translucent nodules slightly above surface. Pulp uniformly pinkish grey. Fibrous trabeculæ prominent. Splenunculus (2·5 × 2 × 1·8) shows similar condition.

Microscopically the chief feature is fibrosis. The capsule is thickened, the trabeculæ are thicker than normal, particularly near the medium-sized veins, and there is a diffuse fibrosis around the venous sinuses, which are dilated. The Malpighian bodies are large, with hyperplastic germ centres, in which the mitotic figures are frequent.

Sparsely scattered in the sections may be seen small perivascular hæmorrhages around the small arteries before they reach the Malpighian bodies. These hæmorrhages present varying degrees of organization and hæmosiderin formation.

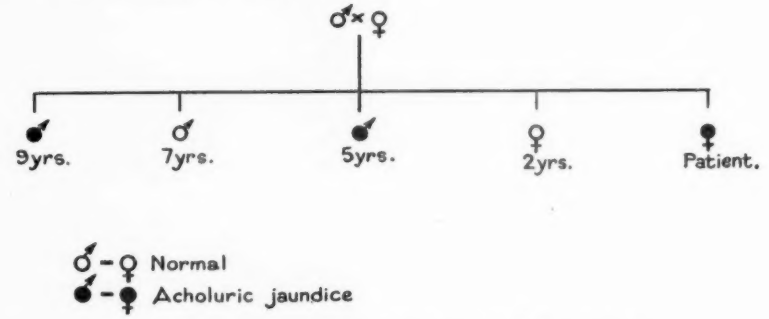
These changes are characteristic of a rather early stage of the enlarged spleens associated with portal obstruction, to which the name of Banti's disease has been applied.

Wedge of fibrous liver (1 × 0·5 × 0·5 cm.). Microscopically typical multilobular cirrhosis with numerous regenerating bile ducts in the bands of fibrous tissue surrounding islands of slightly fatty liver cells.

The boy made a good and rapid recovery from the operation and, when compared with his brother, seems to have made a definite improvement in general health.

Acholuric Family Jaundice in an Infant.—J. C. HAWKSLEY, M.D. (for ROBERT HUTCHISON, M.D.).

B. T., female infant, now 4½ months old, is the youngest of five children. The first and third have both had their spleens removed on account of acholuric jaundice; no other relatives have, so far as is known, suffered from this, and all the immediate relatives have been investigated with negative results.



History of case.—Born 4.10.33; normal labour; full-time infant.

6.10.33. Apparently healthy infant; no icterus, no anæmia, no enlargement of spleen. Blood-count: R.B.C. 7·0 millions. Hb. 140% (Haldane). Fragility test: marked hæmolysis in 0·45% sodium chloride (this normally ceases at 0·39% at 2 days old). Mean diameter of R.B.C. (Price-Jones method) 7·12 μ (normal for this age 7·99 μ, van Creveld).

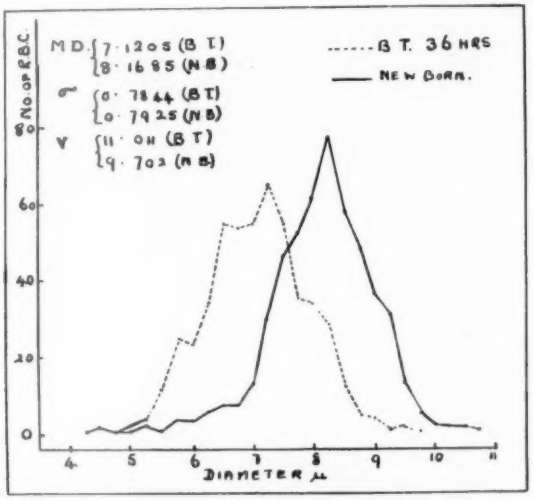
16.10.33. Healthy, no jaundice, no anæmia, no splenomegaly. Blood-count: R.B.C. 6·6 millions. Fragility test: complete hæmolysis in 0·42% sodium chloride; trace of hæmolysis in 0·54%. Mean diameter of R.B.C. 6·67 μ (normal for this age 8·16 μ, van Creveld).

10.11.33. Pallor of skin and mucous membranes. Slight icterus. No splenic or hepatic enlargement. Indirect van den Bergh reaction 2·7 units. Blood-count: R.B.C. 2·6 millions. Hb. 45% (Haldane); reticulocytes 4·2%.

24.11.33. Pallor more marked. Spleen just palpable. Blood-count: R.B.C. 2·5 millions. Hb. 47% (Haldane): reticulocytes 9·7%.

7.12.33. Pallor. Spleen palpable. Icteric. Blood-count: R.B.C. 2·8 millions. Hb. 49% (Haldane); reticulocytes 13·4%; van den Bergh reaction: 1·0 unit, indirect.

18.1.34. Slightly less pale. Icteric. Splenomegaly present. Blood-count: R.B.C. 3·6 millions. Hb. 56% (Haldane); reticulocytes 11·4%. van den Bergh reaction indirect 0·5 unit. Fragility test: complete hæmolysis 0·39% sodium chloride; trace of hæmolysis 0·48%. Mean diameter of R.B.C. 6·84 μ.



Comment.—This case presents two factors of importance. The first is that, knowing of a familial tendency in the direction of acholuric jaundice, it was possible to diagnose the condition some days before there was any clinical evidence of the disease or fall in the number of erythrocytes, both by observing the characteristic increase in fragility of the red cells to hypotonic saline and by a Price-Jones curve, which showed a decreased mean diameter when compared with that of normal newborn infants (see graph). The second factor is the observation that microcytosis (here meaning diminution in mean diameter and not necessarily in cell volume), and increased fragility would seem to be the primary features in this case, the typical syndrome developing subsequently. This supports the hypothesis that acholuric family jaundice is a primary disease of the erythron.

(The van den Bergh and fragility tests were carried out by Dr. W. W. Payne.)

Hepatomegalia Glycogenica with Infantilism in Two Sisters.—R. W. B. Ellis, M.D. (by permission of Hugh Thursfield, M.D.).

Violet M., aged 14 years, and Ivy M., aged 11 years and 10 months.

Family history.—Father alive and well (Wassermann reaction negative); mother died in 1929 from influenzal pneumonia, weight 18 stone, liver being described at post-mortem examination as "much enlarged and fatty." Parents unrelated by blood. The first child (a boy) died in 1918 from influenza, aged 2 years and 9 months, and is thought to have had a "very large spleen" (? liver). No miscarriages.

A step-brother by the father's second wife is microcephalic and mentally deficient; liver not enlarged.

Patients' history.—The patients were not considered abnormal during early infancy, until the large size of the abdomen began to excite comment at about two years of age. The younger girl (Ivy) was backward in walking; she was late in going to school and is considerably below the average in school-work. She is very easily frightened and cries on slight provocation. The elder (Violet) is more nearly normal mentally and emotionally, though one or two years behind girls of her own age at school. Physical development in both cases has been uniformly retarded,

Hepatomegalia glycogenica with infantilism. Control, aged 12 years. Violet, aged 14 years. Ivy, aged 11 years and 10 months.

though both have increased slowly in height and weight since they were first seen five years ago. Both are active and moderately energetic, and in fair general health. Both children are said to have had slight jaundice, of short duration, in the autumn of 1928 (when aged $8\frac{1}{4}$ and $6\frac{1}{2}$ years respectively). They have not been jaundiced at any other time.

When first seen in 1929, the children's measurements were:—

Violet (aged 9 years and 2 months).—Height 45 in. (normal $49\frac{1}{2}$ in.); weight 47 lb. (normal $57\frac{1}{2}$ lb.). Ivy (aged 7 years).—Height $38\frac{1}{4}$ in. (normal 46 in.); weight 35 lb. (normal 48 lb.).

On examination (February 1934).

(I) Violet, aged 14 years. Height 52 in. (normal 60 in.); weight 64 lb. (normal 100 lb.). Circumference of chest (mid-expansion) 26 in., head 19½ in., abdomen (umbilical level) 29 in. A sallow, moderately well-nourished girl with approximately four years' retardation in physical development. The upper and lower central incisors and the first molars are permanent teeth; the permanent lower lateral incisors are in the process of eruption (the corresponding first teeth still being present). The remaining teeth are of the first dentition. The abdomen is somewhat distended by the greatly enlarged firm liver, which extends to one inch below the umbilicus. The spleen is not palpable. No ascites and no jaundice. No telangiectases. No signs of puberty. Wassermann reaction negative.

The urine, on repeated examination, has shown traces of acetone, but no other abnormal constituents.

Biochemical Investigations (Dr. W. W. Payne).

11.10.33.—Lævulose test (30 g. lævulose).

	%		%
Fasting blood-sugar	0·079	1½ hours after	0·084
½ hour after	0·145	2 „ „	0·090
1 „ „	0·087		

13.10.33.—Adrenaline test (5 min. adrenaline).

	%		%
Fasting blood-sugar	0·059	¾ hour after	0·088
¼ hour after	0·072	1 „ „	0·097
½ „ „	0·074		

Blood cholesterol on 18.10.33: 223 mgm. %.

(II) Ivy, aged 11 years and 10 months. Height 46 in. (normal 56 in.); weight 50 lb. (normal 81 lb.). Circumference of chest (mid-expansion) 24½ in., head 19 in., abdomen (umbilical level) 26 in. This child is also pale, and though less robust than her sister, is not abnormally thin. She has approximately the degree of physical development of a child of 7 (i.e. nearly 5 years' retardation). She still has all her first teeth. The liver is enlarged to within one inch of the umbilicus, and has a deep anterior notch. The spleen is not palpable, and there is no jaundice or ascites. Wassermann reaction negative.

The urine has been found to contain traces of acetone on several examinations. Urinary function tests normal.

Biochemical Investigations (Dr. W. W. Payne).

11.10.33.—Lævulose test (25 g. lævulose).

	%		%
Fasting blood-sugar	0·062	1½ hours after	0·077
½ hour after	0·112	2 „ „	0·067
1 „ „	0·092		

13.10.33.—Adrenaline test (5 min. adrenaline).

	%		%
Fasting blood-sugar	0·047	¾ hour after	0·056
¼ hour after	0·055	1 „ „	0·060
½ „ „	0·063		

Blood cholesterol on 18.10.33: 232 mgm. % (on 16.4.29: 350 mgm. %).

Blood-urea on 7.5.29: 20 mgm. %.

Fat in stool on 26.4.29: split fat 10·15%; unsplit fat 7·3% of dried fæces.

Comment. — These two cases show the classical features of Von Gierke's "glycogenic" disease, namely a low resting blood-sugar (in one instance 0·047%), traces of acetone in the urine, a low or delayed rise in blood-sugar following the

injection of adrenaline, hepatomegaly, and infantilism. The few post-mortem examinations that have been carried out on cases of this type indicate that the enlargement of the liver is due to retention of glycogen which cannot readily be mobilized. In these two children the infantilism is singularly perfect, in that they closely correspond in height, weight, proportions, dentition, etc., with children approximately four years younger than their actual age. I would suggest that the infantilism is due to the consistently low resting blood-sugar. It is known that women with early diabetes ("prediabetes")—or in whom diabetic symptoms have not yet manifested themselves but whose resting blood-sugar is slightly though consistently raised—are particularly liable, if they become pregnant, to give birth to overweight infants. It is possible that here we have the reverse process taking place, and that owing to prolonged slight carbohydrate starvation, the tissues are uniformly retarded in their growth and development.

[*The report of other cases shown at this meeting will be published in the next issue of the* PROCEEDINGS *of the Section.*]

Section of Urology

President—A. CLIFFORD MORSON, O B.E., F.R.C.S.

[*February* 22, 1934]

Some Observations on Carcinoma of the Prostate, with Special Reference to Treatment

By F. E. FEILDEN, F.R.C.S.Ed.

ABSTRACT.—It is thought that valuable data should be obtained from a correlation of the clinical and histological features, when dealing with a large number of cases of carcinoma of the prostate. As a result it should be possible to elaborate a system of grouping, each group being characterized by a definite clinical syndrome, pathological features and individual prognosis.

To be of value, a record of the end-results of treatment should be on this basis.

Malignant disease of the prostate is not infrequently associated with benign hypertrophy, and not infrequently arises in a lateral or median lobe.

Cystoscopy may be of definite value in the diagnosis of carcinoma of the prostate.

The perineal method of approach is the operation of choice in the small fibrous type of prostate, especially that which is suspected of being malignant.

The results so far recorded in this country, in the treatment of carcinoma of the prostate by radium, are not encouraging.

As a palliative method of treatment, trans-urethral diathermy should seldom be employed.

The most satisfactory palliative method of treatment is a suprapubic cystostomy. Under certain circumstances, a radical perineal excision is justifiable and satisfactory results may be anticipated.

RÉSUMÉ.—L'auteur croit que des renseignements de valeur résulteraient de la corrélation des caractères cliniques et histologiques quand il s'agit d'un grand nombre de cas de cancer prostatique. Il devrait être possible d'élaborer un système de groupement, chaque groupe étant caractérisé par un syndrome clinique et des signes pathologiques définis et un prognostic individuel.

Pour avoir de la valeur, les résultats définitifs du traitement devraient être régistrés sur cette base.

Les tumeurs malignes de la prostate sont assez souvent associées à l'hypertrophie bénigne, et commencent assez souvent dans un lobe médian ou lateral.

La cystoscopie peut avoir une certaine valeur dans le diagnostic du cancer de la prostate.

La méthode périnéale est l'opération de choix pour les petites prostates fibreuses, surtout celles soupçonnées d'être malignes.

Les résultats du traitement du cancer prostatique par le radium, publiés jusqu'à present dans ce pays, ne sont pas encourageants.

Le traitement palliatif par la diathermie trans-uréthrale ne devrait être employé que rarement.

Le traitement palliatif le plus satisfaisant est la cystotomie suprapubique. Dans certaines circonstances l'excision radicale périnéale est justifiée, et on peut s'attendre à un résult satisfaisant.

ZUSAMMENFASSUNG.—Verf. glaubt dass aus einer Korrelation der klinischen und histologischen Erscheinungen bei einer grossen Zahl von Fallen von Prostatakarzinom wertvolle Angaben erlangt werden könnten. Aus diesen sollte es möglich sein eine Gruppierung auszuarbeiten, in welcher jede Gruppe durch bestimmte klinische und pathologische Eigenschaften und eine individuelle Prognose charakterisiert wäre.

Um wertvoll zu sein müssten die Erfolge der Behandlung auf dieser Grundlage aufgezeichnet sein.

Bösartige Geschwülste der Prostata sind nicht selten mit gutartiger Hypertrophie verbunden und gehen nicht selten von einem lateralen oder medialen Lappen aus.

Die Zystoskopie kann in der Diagnose des Prostatakarzinoms ein gewisser Wert haben.

Für kleine, fibröse Prostaten, besonders wo ein Verdacht auf bösartige Geschwulst besteht, ist der perineale Weg die Methode der Wahl.

Die bisher in diesem Lande mitgeteilten Erfolge der Radiumbehandlung des Prostatakarzinoms sind nicht befriedigend.

Als palliative Behandlung sollte die transurethrale Diathermie selten benützt sein.

Die beste palliative Behandlung ist die suprapubische Zystotomie. Unter gewissen Bedingungen ist die radikale perineale Exzision berechtigt, und gute Erfolge können davon erwartet sein.

FOR the purposes of this communication I have reviewed my notes of 140 consecutive prostatectomies; of this number 25, or approximately 18%, were clinically or pathologically carcinoma.

In reviewing these cases I have been impressed by the fact that in dealing with a large number of cases, a correlation of the clinical and histological features should result in much valuable information, and that it should be possible to group carcinoma of the prostate, each group having its own clinical syndrome, pathological features, and individual group prognosis.

Cancer of the prostate varies widely in its clinical manifestations. For example, in one case there may be a small nodule discovered in the prostate, apparently confined within the capsule, yet there are extensive secondaries in bone, lungs or lymphatics. In another there may be extensive local spread, but little, if any, general metastasis.

In most cases the disease remains confined within the capsule for a considerable time (this fact is important when considering treatment); eventually, however, invasion of the connective tissue spaces of the stroma and of the capsule occurs. Backward spread is, to some extent, prevented by the anterior layer of the recto-vesical fascia. By the spread of the growth along the walls of the vasa and vesiculæ, the ureters and base of the bladder become involved, and in its course along the lateral ligaments of the bladder it reaches the pelvis, the lumbosacral nerve plexus and the lumbar group of lymphatics.

For convenience of description I have divided my 25 cases into three clinical groups:—

(1) Unsuspected (six cases). (2) Suspected (four cases). (3) Undoubted (fifteen cases).

In the first group the signs and symptoms were essentially those characterizing benign enlargement of the prostate. The renal function tests were uniformly less satisfactory than in the remaining two groups.

Nothing suggested a malignant tumour. With one exception, the histological picture was that of an early adenocarcinoma associated with a simple hypertrophy.

It seems evident, therefore, that a simple adenoma may undergo malignant changes. Such cases appear to have the best prognosis and seem, as a rule, to run a less malignant course.

It is of interest to note that in five of the six cases the carcinoma was confined to a lateral lobe.

Ferguson [1], in referring to the lobar origin of prostatic cancer, states, that in 1,426 cases, collected from papers by McGrath, Wade, Bugbee and others, 183, that is 12·8%, early carcinomata were found in prostates which had been removed for benign enlargement; and in each case it was situated in a median or lateral lobe. With regard to the frequency of the unsuspected type of case,

according to Albarran and Hallé [2], as many as 20% of cases of supposed simple enlargement of the prostate are malignant.

The exception in the histological picture, to which I have already referred, proved to be a highly cellular, rapidly growing carcinoma, in which, histologically, there was little evidence of any alveolar arrangement. Six weeks after the prostatectomy, the patient died from a left-sided hæmothorax, the result of a secondary deposit in the lung. In this particular case the prostatic growth was so cellular that it was soft in consistence. The soft forms, and those composed mostly of intra-acinous growth, may be missed, whereas the hard, fibrous prostates, the result of chronic inflammation, may stimulate carcinoma.

In the remaining five cases the patients are alive, and apparently well, with no evidence of local recurrence; nor do they complain of any urinary disturbance. The earliest case was operated upon rather more than six years ago.

In the second group, namely the suspected cases, the chief symptoms complained of were difficulty in micturition, perineal pain, and, in one case, pain referred to the tip of the penis. The residual urine was moderate in amount, and the blood-urea was low in comparison with that in the preceding group. Per rectum, the prostate was felt to be slightly larger than a normal prostate; induration was definite, but no appreciable infiltration could be detected. X-ray examinations were negative for bone changes. On these findings a diagnosis of fibrosis of the prostate was made, with a query as to malignancy. Histologically, the sections showed a definitely infiltrating carcinoma of a prostate which was the seat of a chronic prostatitis.

In this type of case, an accurate diagnosis is often of considerable difficulty. One must of course exclude such conditions as tuberculosis and prostatic calculi.

I am of the opinion that cystoscopy may be of considerable help in diagnosis. In carcinoma of the prostate, when the instrument is passed, it appears to be gripped in the posterior urethra, and passes with a peculiar dry grating sensation, quite characteristic. The cystoscopic picture may reveal a few irregular projections, and the trigone may be raised by the growth. On rare occasions an ulcer may be seen, due to the invasion of the bladder by growth.

If operation is decided upon, the more rational approach appears to be the perineal route. Under these circumstances one has the advantage of direct observation and palpation, and a decision can be more easily reached as to the better method of treatment to adopt, i.e. removal or radium.

Certain technical difficulties, however, exist, and even in the hands of experts the operation may be attended by unpleasant consequences. It has been stated by Wildbolz [3] when referring to perineal prostatectomy, that out of 300 cases, injury to the rectum occurred in seven, and in eleven some urinary incontinence persisted.

In the four cases under review I performed perineal prostatectomy. In two of these there has already been local recurrence, necessitating suprapubic drainage. Both were operated upon just over a year ago. The other two patients who were operated upon two years and five months, and three years ago, respectively, are both well and have no urinary symptoms or evidence of local recurrence.

My personal experience of the treatment of prostatic cancer by radium is very limited.

The results, so far recorded, are not such as to raise enthusiasm. However, I note that Barringer [4] is of opinion that from 5% to 10% of prostatic carcinomata can be controlled by radium sufficiently to lead one to think the patient is cured.

With regard to the third group in my series—the undoubted cases: clinically, this group was characterized by widespread pain and considerable urinary distress. In two of the fifteen cases bone metastases were demonstrated. According to Kaufman [5] the incidence of bone metastases is as high as 25% of all cases. In the majority, contrary to expectation, the blood urea was not above 50 mgm. This

figure is of interest when compared with the renal function tests which characterized the cases in the unsuspected group. On rectal examination, in each case the prostate was found to be moderately large, hard, nodular, and firmly fixed to the surrounding structures. The residual urine varied from 3 oz. to 8 oz., but in four cases there was complete retention. As a rule, the patient's general condition was stated to be good, emaciation being the exception. In each case the section showed an advanced carcinoma, characterized by the absence of any alveolar arrangement of the cells, marked infiltration of the stroma, and in some cases by invasion of the perineural lymphatics. The perineural lymphatics in tumours of the prostate are of special interest. According to Russell Ferguson [6], who investigated 205 post-mortem cases of prostatic cancer, the perineural lymphatics were invaded by the growth in 52%. This author suggests that pain, in the absence of bony metastases, is probably due to the actual infiltration of the lymphatics of the nerve sheaths.

In two cases radium was inserted by the perineal route; in both these cases the patients died within three months, from uræmia. In three, the obstruction was removed by transurethral diathermy, and although the immediate result was good, a subsequent suprapubic drainage was necessary. In the remaining ten cases nothing but a suprapubic cystostomy was attempted.

Apparently transurethral diathermy is an ideal method of delaying the need for a suprapubic bladder drainage. In many cases, however, the period of delay is, I am convinced, very short. The obstruction rapidly recurs, and a second attempt at the operation results in failure, owing to the fact that the instrument cannot be passed. I am inclined to think that by this method of treatment the growth is stimulated, rapid extension occurs, and the bladder is involved earlier than it otherwise would be.

The majority of surgeons have come to the conclusion that the only justifiable form of treatment for any case of prostatic cancer is permanent suprapubic bladder drainage. This attitude is in marked contrast to certain authoritative opinions in America and on the Continent, where radium therapy, X-ray therapy, or an extensive radical excision is favoured.

In 1929 Young [8] described a radical perineal operation which he devised, for carcinoma of the prostate, for which he claims good results. The figures quoted were: In twenty-seven cases operated upon seven years or more ago, 57% have lived for periods of seven to thirteen years.

The value of the results of any particular method of treatment must depend upon statistics, but the comparison of remedies for carcinoma of the prostate at present is of little value, owing to the difficulties of classifying prostatic growths.

As regards radical excision, I am inclined to think that, if the diagnosis can be made before the growth has burst through the capsule, and in the absence of metastases, it is the duty of the surgeon seriously to consider an attempt at radical excision of the growth, based on modern surgical principles, and I think one may reasonably expect satisfactory results in a few very carefully selected cases.

In conclusion, I wish to acknowledge my indebtedness to Dr. H. M. Galt of the Royal Sussex County Hospital, who has supplied the histological reports on my cases.

REFERENCES

1 Ferguson, Russell S., *Am. Journ. of Cancer*, 1932, xvi, 784.
2 Quoted in Thomson-Walker's "Genito-Urinary Surgery," London, 1914, 751.
3 Wildbolz, Hans, *Lancet*, 1927, (i), 1007.
4 Barringer, B. S., *New Eng. Journ. of Med.*, 1928, cxcviii, 117.
5 Kaufman, L. R., *Surg. Clin. of N. Amer.*, 1929, ix, 701.
6 Ferguson, Russell S., *Amer. Journ. of Cancer*, 1932, xvi, 790.
7 Bumpus, H. C., *Surg. Gyn. and Obst.*, 1921, xxxii, 31.
8 Young, Hugh H., *Am. Journ. of Surg.*, 1929, n.s., vi, 672.

Mr. H. P. WINSBURY-WHITE: Up to the present the results from radium implantation do not encourage us to feel that this method of treatment of carcinoma of the prostate is going to be a success.

Suprapubic cystotomy is the only operative procedure from which I have personally known any benefit to be obtained, and this benefit is, of course, only of a palliative nature.

[*March* 22, 1934.]

Injury to Bladder caused by in-dwelling Gum-Elastic Catheter.—F. MCG. LOUGHNANE, F.R.C.S.

W. J., aged 52. History of frequency and dysuria. Cystoscopy and urethroscopy revealed the presence of a prostatic bar. Endoscopic resection was performed, three large pieces being removed. Three days later patient complained of hypogastric pain, and there was œdema of the penis and scrotum. Next day the bladder was opened for drainage. There were no clots present, but there was sanious fluid in the cave of Retzius. No improvement followed; the patient began to hiccough, had irregular action of the bowels, occasionally vomited after meals, and died four days later.

Post-mortem report.—The peritoneal cavity contained a large quantity of purulent fluid. The small intestine was adherent to the roof of the bladder, which was perforated. There was a large necrotic area, as shown in the specimen. This was presumably a pressure necrosis caused by the in-dwelling, hard, gum-elastic catheter. There was no sign of any inflammatory reaction around the prostate.

An Inflatable Intestinal Bag as an Addition to the Technique of Uretero-Colostomy

By JOHN EVERIDGE, F.R.C.S.

ONE difficulty of the Coffey operations is that associated with the formation of the submucous bed for the ureter. A neat incision on an unsupported surface is not easy, and here is especially so, on account of the rugosity and vascularity of the bowel wall. By introducing a rubber bag through the sigmoidoscope previous to opening the abdomen, certain advantages may be claimed. The bag, after introduction, is distended with air or fluid with a syringe through its long filling tube. The sigmoidoscope and introducer are then removed. When the abdomen is opened the section of bowel for the anastomosis is rendered obvious; and, having prepared the ureter, the bowel wall is incised upon the distended bag, which will have been previously manipulated into the desired position. If Coffey No. 1 is proceeded with, the stitch drawing on the ureter is easily insinuated between the bag and the bowel wall, and fixed in the usual place, one inch below the anastomosis. The bag is then allowed to collapse, and the implacement and fixation of the ureter by sutures is carried out in the usual way. If Coffey No. 2 is being performed, the needle threaded to the stitch attached to the catheter transfixes a tiny knuckle of collapsed bag drawn up through the stoma. An assistant then exerts traction on the filler tube and so draws out the catheter, and the ureter is thus brought naturally into its bed.

It has been found that in addition to facility for formation of the bed, the size of the stoma may be more accurately controlled. The degree of bowel distension produced by the bag renders the operative field, and especially the region of the stoma, less liable to contamination, since fæces (from imperfect preparation) are displaced, free mucus in the bowel is kept away and the mucous coat is squeezed and flattened out. A bowel clamp, usually employed, is unnecessary in this technique.

Adenoma of Kidney.—MALCOLM BAILLIE, M.B.

The specimen is from a woman, aged 25, who had two attacks of pain in the back with hæmaturia. Excretion urography showed filling defect of the upper and middle calyces of the left kidney. Three months later further hæmaturia was accompanied by typical left renal colic, and blood was seen coming from the left ureter. Instrumental pyelography showed an identical filling defect. Nephrectomy was performed.

The section shows an alveolar adenoma developed from adult renal tubules but with absence of definite lumina.

The specimen has the unusual features of an intrapelvic position, a large size ($1\frac{1}{2}$ in. in diameter), and a colour like that of the renal parenchyma.

JOINT DISCUSSION No. 3

Section of Epidemiology and Section for the Study of Disease in Children

Chairman—Dr. J. D. ROLLESTON, President of the Section of Epidemiology

[*January* 26, 1934]

DISCUSSION ON THE ÆTIOLOGY OF ACUTE RHEUMATISM AND CHOREA IN RELATION TO SOCIAL AND ENVIRONMENTAL FACTORS

Dr. J. Alison Glover: As a starting point I will refer to a document with which I am sure you are all familiar—the Report [17] of the Child Life Committee of the Medical Research Council on "Social Conditions and Acute Rheumatism," which appeared in January 1927. This well-controlled and thorough investigation was the combined work of three teams of observers at St. Thomas's Hospital, the Hospital for Sick Children, Great Ormond Street, and the Royal Hospital for Sick Children, Glasgow. The medical and social histories of 721 rheumatic families, 200 control families and 2,000 school children living in Poor Law schools, were ascertained. The possible medical factors investigated included familial incidence and heredity, the familial incidence of sore throat and throat conditions (especially tonsillectomy). The possible social factors investigated included maternal care, exposure, sleeping accommodation, clothing, cleanliness and distance from school, condition, birthplace, occupation and income of the parents, housing conditions, and the sites of houses. Yet of all this thorough and patient work "the findings are largely negative." To quote Dr. Still's own words:—

> "The comparison between the social conditions under which the rheumatic and control children were living has failed to reveal any differences or any factor in the social circumstances of the rheumatic children which might be described as causative . . . The maternal care was found to be inferior, the amount of subjection to exposure appeared to be greater, and the clothing less good in the case of the rheumatic children. The health of the parents was also not so good in the rheumatic as in the control families. In the St. Thomas's Hospital data a higher proportion of rheumatic than control families were found in houses situated under 50 ft. above sea-level."

The evidence as to whether a "rheumatic type" of child could be distinguished in relation to the pigmentation of hair and eyes was also so conflicting as to be practically insignificant.

Perhaps the most important positive finding was the low incidence found in the children living in the Poor-Law residential schools, discounted though it was to some very slight degree by the fact that a child with recognized heart disease or chorea would not presumably be sent to these schools. Nevertheless, the fact that only 1% of these children were affected suggests that children living under the better general hygiene of such institutions are much less frequently attacked than children of the same class living under the ordinary conditions of a poor home.

The most important factor not dealt with in the Committee's Report was *diet*, whilst *urbanization* was another factor which could not be assessed by the Committee, for their investigations were made in London and Glasgow. The importance of this well-known factor, and especially the high incidence in the city of Bristol, were the chief lessons of the report [2A] of the Bristol and three Counties investigation into rheumatic heart disease, the investigation inspired by the late Dr. Carey Coombs.

Progress in the seven years since the report.—Though seven years have elapsed since the publication of this Report, and though much other work on the same subject has since been published, it must be confessed that the social and environmental—as well as the bacteriological—factors in the ætiology of acute rheumatism still form one of the great enigmas of preventive medicine.

Has this last seven years brought us any progress through the difficulties revealed by the Report?

"*Rheumatic type*" *of child unrecognizable.*—That no "*rheumatic type*" of child can be distinguished by bodily conformation, physical type, or pigmentation, has, I think, been proved by Gray Hill and Allan [9] and confirmed quite recently by M. Young and Bonnard [21].

Poverty.—As to the *degree of poverty* which causes the highest incidence, the Child Life Committee expressed the opinion that "if hospital patients are divided into three classes according to the degree of poverty, the poorest of these three, the very poor and destitute, show a lower incidence of rheumatism than the other two." This view had been published in slightly different terms in the first Report [2B] of the British Medical Association's Committee on Rheumatism some six months before the Child Life Committee's report, and it is still accepted by many (perhaps the majority) of English physicians. Nevertheless, a minority, in which I find myself, believe that the true incidence of acute rheumatism is directly proportional to the degree of poverty. Fenton and Aitken [10] in their admirable Annual Reports of the Kensington Rheumatism Scheme, Gray Hill [8] at Queen Mary's Hospital, Carshalton, and Campbell and Warner [3] at Guy's Hospital and at Woolwich, all find that the poorest are the most commonly affected.

Notwithstanding this slight divergence of opinion, nearly all are agreed that poverty remains the social factor at the root of nearly all the other social environmental and dietetic factors, and that the incidence of acute rheumatism is twenty or even thirty times as great upon the children of the poor as upon the children of the well-to do. The children of the poorest have perhaps one doubtful advantage—their life is largely spent in the open-air of the street; as a child population, moreover, probably a larger proportion of the least resistant have succumbed to other diseases before they reach the age at which rheumatic infection becomes apparent.

Ætiological significance of infection.—But perhaps the most hopeful progress is in our increased knowledge of the ætiological relationship of *Streptococcus pyogenes* to acute rheumatism, due to the work of F. Griffith, Collis [5], Sheldon [16], Bradley [1], Schlesinger [14], and Todd [19] in this country, and the work of Coburn [4] in the United States. This work affords us a fresh view-point of the social and environmental factors. By it the theory of the causal relationship of streptococci to acute rheumatism propounded by Poynton and Paine [12] in 1900 has been greatly strengthened and more accurately defined. The close connexion between tonsillitis and acute rheumatism, the striking seasonal variation, the rarity of the disease in certain climates, and the occasional small epidemic, have all long been known, but prior to the above-mentioned investigations, hardly any systematic bacteriological study of the waves of tonsillitis and the carriers associated with them has been described.

Coburn's [4] work showed first that there is a direct correlation between the geographical and seasonal distribution of hæmolytic streptococcal throat infection and acute rheumatism; secondly, that poverty and unhygienic conditions favour both hæmolytic streptococcal infection in the throat and the incidence of acute rheumatism; thirdly, that bacteriological studies of upper respiratory infections followed by localized outbreaks of rheumatism, demonstrate a close relationship between the advent of hæmolytic streptococcus in the throat and the outbreak of rheumatic fever in susceptible individuals, whether in families or in institutions; and

fourthly, he showed by a four years' bacteriological study of the throat flora in ambulatory rheumatic subjects, that the individuals who escape respiratory disease remain free of rheumatic manifestations, whilst, conversely, the majority of those rheumatic subjects who had a tonsillitis or pharyngitis due to hæmolytic streptococci had a recurrence of rheumatism within three weeks of the throat infection.

In subsequent studies, Coburn, in association with E. W. Todd [19] in England, showed that at the onset of an attack of acute rheumatism there occurs a rise in the antistreptolysin titre of the patient's serum. This titre is much higher than in normal subjects or in patients with bacterial infection other than hæmolytic streptococcus, and is strong evidence of recent infection with hæmolytic streptococcus.

Schlesinger and Signy [15] have demonstrated streptococcal precipitins in the blood of rheumatic patients, following acute streptococcal throat infections, but not appearing until the second to the fourth week from the onset of the nasopharyngeal infection and foreshadowing a tendency to a relapse of acute rheumatism. Coburn has similar findings.

Collis [5] and Sheldon [16] at Cheyne Hospital and Schlesinger [14] at West Wickham, working in special rheumatism wards, showed, amongst other points, that relapses of acute rheumatic arthritis or carditis are often preceded by an initial fever at an interval of one to four weeks; that this fever is usually demonstrably due to nasopharyngeal infection with hæmolytic streptococci, and that nasopharyngeal infections, other than hæmolytic streptococci occurred, but did not cause recurrence of rheumatism even in rheumatic subjects.

Bradley [1] dealing, at a boarding public school, with several small rheumatic outbreaks, which followed waves of tonsillitis due to at least two distinct serological types of hæmolytic streptococcus, suggests that the preliminary acute and possibly transitory throat infection should be called the "precursor fever": that hæmolytic streptococci of various types cause it, and that they are spread by droplet infection. Rheumatism, he suggests, occurs in those who, being incompletely immunized by a first contact with a rheumatism-producing streptococcus, develop a hypersensitiveness (allergy) to that organism. Subsequent contact with allergen (endotoxin) precipitates the rheumatic attack. Control of rheumatism requires the prevention of the precursor fever. Acute rheumatism, he sums up, is a manifestation of abnormal tissue responses to acute and repeated contact with streptococci commonly spread by droplet infection.

The work of all these observers, which time has compelled me to condense to a misleading brevity, seems, if confirmed, to afford us a fresh insight of the effect of social environmental factors on acute rheumatism. Behind the veil of visible environment, the poor, damp, and overcrowded house in the low-lying site (though these factors remain as potent for evil as before), there is revealed the unseen environment of infection by the hæmolytic streptococcus. This can be gauged by the attack-rate of tonsillitis and by the height of the hæmolytic streptococcal carrier-rate. A high carrier-rate indicates not only more carriers numerically, but almost certainly a higher proportion of dangerous, heavily infected or "pure plate" carriers, and usually the prevalence of one epidemic strain. As a less obvious consequence, it suggests the presence of individuals sensitized to the hæmolytic streptococcal toxins.

This environment, this high potential of hæmolytic streptococcal infection, is facilitated by overcrowding, deficient ventilation, and dampness, and often by a concurrent catarrhal disease such as measles or influenza, though the latter do not themselves (i.e. without a complicating streptococcal infection) appear to provoke the rheumatic attack or outbreak. The source of infection in the person of a chronic carrier can seldom be identified, save perhaps in families, a subject to which I shall refer later.

As in other infectious diseases in which the number of immunes is very high compared with that of susceptibles, the ætiology of acute rheumatism is only to be

discerned when cases occur in epidemic form; in rheumatism as in meningitis, more is to be learnt from an epidemic of a dozen cases than from a hundred apparently sporadic cases of so-called basal meningitis.

Institutional epidemics.—Many observers have described small outbreaks of acute rheumatism in semi-closed communities of various kinds. In 1930 I described three in training depots [6], and in 1931 Dr. Griffith [7] and I described two in public boarding schools. Both of these latter showed well the factor of the "epidemic strain" of hæmolytic streptococcus, but it is to the second of these I should like to refer for a moment, for, although the numbers are so small that a chance coincidence cannot be excluded, one feature in it suggests the hypersensitiveness due to a previous infection with hæmolytic streptococcus stressed, by Bradley. Here, in a boy population of about 500, the cases of acute rheumatism were associated with an epidemic of tonsillitis due almost entirely to one serological strain of hæmolytic streptococcus carried on from one Christmas term to the succeeding Lent term. Four cases of acute rheumatism occurred in the Christmas and three in the Lent term. Of the four cases occurring in the Christmas term, three were in one dormitory of 48 boys. Eight boys in this dormitory suffered from severe tonsillitis, all being infected with the epidemic strain. Four only of all the 48 boys had a previous history of scarlet fever (none less than seven years previously). One of these four boys escaped both tonsillitis and acute rheumatism, but in all the other three acute rheumatism followed tonsillitis. In none of the five other tonsillitis patients, who had not a history of previous scarlet fever, did rheumatism occur.

The floor space in the dormitory was large—77 sq. ft. per bed—owing to its great width, but the wall space per bed was only 4 ft. 9 in. The ventilation was unsatisfactory, the ratio $\frac{\text{open-window-area}}{\text{floor area}}$ being only $\frac{1}{3\frac{1}{2}}$.

Whittingham [20] has recently shown at Halton that R.A.F. apprentices who have a history of having had scarlet fever are more liable (in the proportion of three to two) to contract tonsillitis or rheumatism than those who have no such history.

Conversely, in view of the great danger of cross infection or re-infection with other strains of hæmolytic streptococcus, shown by Griffith to exist in scarlet fever wards, we have elsewhere [7] raised the question whether a rheumatic child should ever be admitted to a scarlet fever ward considering of the increased risk of recurrence of his rheumatism incurred.

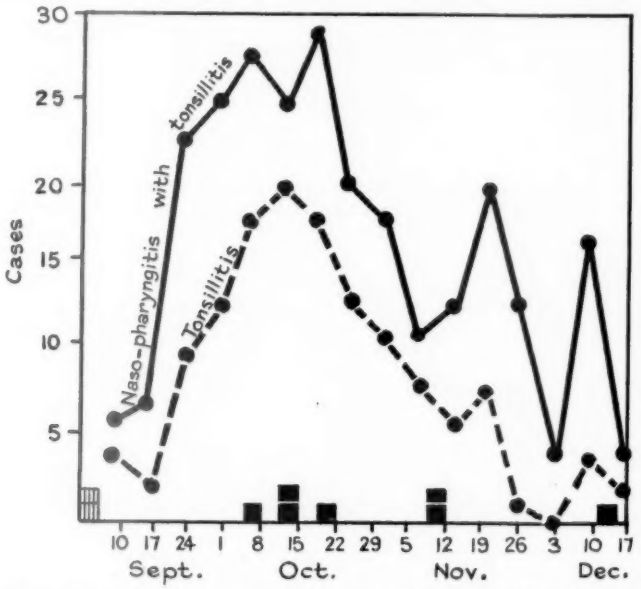
In the autumn of 1932 another outbreak occurred in a large residential school which had been free from any case of acute rheumatism for two years. An epidemic of tonsillitis and nasopharyngitis began about September 20, reached its maximum about the middle of October, and died away at the end of November. The attack-rate for the term of tonsillitis was 16%, four times the usual amount, whilst for febrile nasopharyngitis, including tonsillitis, it was 31%. A boy who had previously had chorea had a recurrence two days after the beginning of term, whilst another boy developed chorea for the first time on the same day; but it is unlikely that these patients were the source of infection as they were immediately isolated. Apart from these two cases of chorea, six cases of acute rheumatism occurred about the peak of the nasopharyngitis epidemic, and one case late in December. The dates on which these cases occurred were consistent with the theory of the existence of a lag period of some fourteen days' average duration.

The non-contact carrier-rate of hæmolytic streptococcus is known to have been exceedingly high during the period corresponding to the peak of the nasopharyngitis and tonsillitis epidemic and to the occurrence of the cases of acute rheumatism. It is also known that by December it had fallen to more normal limits; in other words, the "carrier epidemic" wave had sunk with the abatement of the nasopharyngitis tonsillitis "case epidemic" wave.

This high potential of hæmolytic streptococcal infection was probably due, in the main, to conditions in the sleeping quarters. The dormitories each contained large

numbers of beds, a fact which seems to steepen an epidemic wave and to increase the virulence of infection. The total floor space was sufficient to give about 50 sq. ft. per bed, but owing to the arrangement of beds in rectangular blocks, the "effective" floor space was much less, and the side interval between beds was about 1 ft. 8 in. Bed charts showed clear evidence of bed-to-bed infection. Here is a weekly incidence chart which in the sequence of events closely resembles that of the larger epidemic at the Naval Training Depot, which I have described at length elsewhere [6]. One point of interest in this, the most recent epidemic, is that the children, though of the elementary school class, were, as a population, almost as highly tonsillectomized (47%) as are the children found in boarding schools of the wealthier classes (average 55%).

I am greatly indebted to the School Medical Officers who have supplied the information with regard to these two outbreaks, and regret that owing to the confidential nature of these inquiries, conducted under the ægis of the Committee



A small epidemic of acute rheumatism in a residential school with 863 boys. Weekly incidence of admissions to school sanatorium.

Continuous line = total weekly admission for nasopharyngitis (i.e. *including* tonsillitis).
Dotted line = weekly admissions for tonsillitis.
Black squares (each) = one case acute rheumatism.
Shaded squares (each) = one case chorea.

of the Medical Research Council for the Investigation into Epidemics in Schools, I am unable to give their names, but I wish to thank the Council and the Committee for permission to use these figures.

An admirable study of the environmental factor in rheumatism in mentally defective children at The Fountain Hospital has recently been published by J. L. Newman [11], who found a remarkably low incidence despite a low, damp site for the Institution. The low incidence seems to be correlated with the remarkably good ventilation of the wards, and with the fact that each patient has, on the average, 130 sq. ft. of floor space.

Familial infection.—Paul and Salinger [13], studying 15 rheumatic families, found that "non-specific" respiratory infections occurred before the appearance of characteristic acute rheumatism, that both primary attacks and recurrences in certain members of the family have often occurred simultaneously with acute rheumatism or not infrequently with sore throat, bronchitis, bronchopneumonia and skin rashes in other members. Swift [18] gives two excellent examples of similar family infections. He quotes a case in which the mother of a rheumatic child frequently had a sore throat a short time before the appearance of a relapse in the child. Following the removal of badly diseased tonsils in the mother, her attacks of sore throat ceased, and since then the child has been free from recurrences of rheumatism.

To quote again from the Report [17] of the Child Life Committee, it was stated that "The health of the parents was also not so good in the rheumatic as in the control families."

Regular continuous investigation of the throat flora of every member of a number of rheumatic families, together with an adequate control in non-rheumatic families, correlated with an investigation similar to that of Paul and Salinger, would seem well worth while. Contact examination, a well-recognized procedure in the prevention of tuberculosis, has been neglected in the prevention of acute rheumatism, at least as regards the throat flora, and perhaps even the clinical examination of the throats of the contacts.

If I have laid emphasis on one aspect—the infective—of the matter, it is because I well know that the others will be amply dealt with later. My task seemed to be to suggest that, whilst the theory of the hæmolytic streptococcal environment in no way diminishes our appreciation of the practical importance of the more obvious social and environmental factors, yet it may aid us in their interpretation.

The fact that many of the environmental problems of tuberculosis remain unsolved, despite our much more certain knowledge of the tubercle bacillus, warns us against any undue optimism that the theory has completely solved all (or indeed any) of the environmental problems of acute rheumatism. But if optimism is to be avoided, equally we may say, reviewing the seven years since the Report appeared, that there is no need for pessimism. If we have yet far to go, we seem to have moved no small distance towards our goal—the understanding of the complicated social and environmental factors in the ætiology of acute rheumatism.

REFERENCES

1 Bradley, W. H., *Quart. Journ. Med.*, 1932, xxv, 79; *Proc. Roy. Soc. Med.* xxv, 43-49.
2 *British Medical Journal*, 1931 (ii), 18, Supplement, p. 37; 1926 (ii), Supplement, p. 8.
3 Campbell, M., and Warner, E. C., *Lancet*, 1930 (i), 61.
4 Coburn, A. F., "Factor of infection in the rheumatic state," 1931.
Coburn, A. F., and Pauli, R. H., *Journ. of Exper. Med.*, 1932, 56, v, 609-676.
5 Collis, W. R. F., *Lancet*, 1931 (i), 1341.
6 Glover, J. A., *Lancet*, 1930 (i), 499.
7 Glover, J. A., and Griffith, F., *Brit. Med. Journ.*, 1931 (ii), 527.
8 Hill, N. Gray, *Brit. Journ. of Child. Dis.*, 1930, xxvii, 171.
9 Hill, N. Gray, and Allan, M., *Brit. Med. Journ.*, 1929 (ii), 14.
10 "Kensington Rheumatism Scheme," *Annual Reports*, 1929, *et seq.*
11 Newman, J. L., *Journ. State Med.*, 1933, xli, 590.
12 Poynton, F. J., and Paine, A., "Researches on rheumatism," 1913.
13 Paul, J. R., and Salinger, R., *Journ. Clin. Invest.*, 1931, 33.
14 Schlesinger, B., *Arch. Dis. Childhood*, 1930, xxx, 411.
15 Schlesinger, B., and Signy, A. G., *Quart. Journ. of Med.*, 1933, xxvi, 255.
16 Sheldon, W., *Lancet*, 1931 (i), 1337.
17 "Social conditions and acute rheumatism," 1927, Medical Research Council, Special Report Series, No. 114.
18 Swift, Homer F., *Amer. Heart. Journ.*, 1931, vi, 625.
19 Todd, E. W., *Brit. Journ. Exper. Path.*, 1932, xiii, 248.
20 Whittingham, H. E., *Journ. Roy. San. Inst.*, 1933, liv, 168.
21 Young M., and Bonnard, A., *Journ. Hygiene*, 1933, 435.

Dr. Reginald Miller: When we consider the causative factors of juvenile rheumatism we have in our minds three sets of such factors: (1) the actual bacterial cause circulating in the blood-stream, (2) the predisposing factors, such as class incidence, and (3) the exciting factor, such as an attack of scarlet fever, or getting wet through. In our theoretical discussions it is important that we should try to keep these distinctions clear, otherwise it is impossible for us to appreciate exactly the significance of any so-called "cause" of rheumatism as we debate it. In practice these distinctions matter less. If, as we think, the actual cause of the disease is a micro-organism normally present in the alimentary tract, the predisposing and exciting causes gain in importance, as they are the factors most under our control.

The first serious study of the environmental causes of juvenile rheumatism appeared in the first report of the British Medical Association Committee on Rheumatic Heart Disease in 1926, nearly a year before that of the Medical Research Council which Dr. Glover has taken as a "convenient base line"; and I like to think that in opening a discussion on heart disease in early life at the Medicine Section of the British Medical Association annual meeting of 1923, I had put forward a plea for an investigation by a committee of the causes of the class-incidence of juvenile rheumatism. The particular value of the British Medical Association Reports of 1926 and 1927 lies in this fact: that, although sections of these were signed by individual members, the Report as a whole were sponsored by, and reflected the views of, a Committee which largely consisted of physicians thoroughly experienced in the problems of juvenile rheumatism. And the point that I wish to make here is that there is in clinical medicine an extensive, I would almost say a massive, knowledge of the natural history of the disease, and for my own part I think that such knowledge, even in matters of considerable detail, is extremely unlikely to be wrong. When, therefore, the problems of juvenile rheumatism are discussed from the more novel angles of epidemiology and public health, it is impossible not to test the views expressed by their agreement with what is known on the clinical side of the natural history of the disease.

I propose to consider some of the problems still outstanding in connexion with the subject, and to see how they fit into our clinical knowledge of juvenile rheumatism.

Poverty.—It is agreed that juvenile rheumatism is essentially a disease of the poorer classes, but is it truly a "poverty" disease, in the sense that destitution, deprivation, overcrowding, and squalor determine its class-incidence? This is precisely what most investigations have failed to find; on the contrary they seem to show that the highest incidence occurs in the upper and middle strata of the poor rather than in the lowest. Dr. Glover holds that these results are due to the fact that cases were traced from voluntary hospitals, and that the very poorest do not frequent such hospitals, but drift to the Poor-Law hospitals. I think that voluntary hospitals, particularly those for children, would be very loath to agree with this; and it seems most unlikely, in view of the fact that the voluntary hospitals have out-patient departments and the Poor-Law hospitals have not. But even if we accept Dr. Glover's view that the hospital figures on the poverty question are vitiated, on account of their drawing their patients from the upper strata of the poor, it would be interesting to know why the Poor-Law figures are not vitiated on account of their drawing their patients from the lowest strata of the poor.

Too much, perhaps, has been made of this point of dispute, for reasons to which I refer later. The truth is that so much juvenile rheumatism is found in the upper and middle strata of the poor that clinicians cannot accept the view that its frequency is determined merely by the degree of poverty. The accompaniments of some grade of poverty seem all-important in the production of rheumatism in children, but destitution, overcrowding, and squalor cannot be regarded as the determining ætiological factors.

Damp.—The association of damp and cold is another of the environmental factors in the mass-production of juvenile rheumatism, but again, is not the determining factor. When I first put forward this rather obvious point, it was subjected to a good deal of criticism. Yet I do not think that it can be otherwise than true. We know that the incidence of juvenile rheumatism tends to be high in low-lying districts round water courses; to be high in the temperate zone, and rare in hot countries; to be particularly high in the cold damp months of the year; and to be high in basement-dwellers. Further we know that exposure to cold and wet is a definite exciting cause of an attack in some cases, and that rheumatism is particularly associated with catarrhs and acute and chronic infections of the tonsils. And lastly, we know that to move children of the rheumatic stratum out of their homes and transfer them to Poor-Law boarding schools is sufficient to prevent the appearance of rheumatic infection amongst them. Therefore to hold that cold damp is a predisposing cause of rheumatism is in line with our knowledge of the disease, though if it is preferred to regard it as an "unmasking" rather than a "predisposing" factor I should be content.

To what degree living in damp, cold houses predisposes to rheumatism is a difficult question: clearly it is not the determining factor. My own experience leads me to think—though I do not wish to press this point—that this factor does sometimes explain the class-incidence of the disease, and that it is possibly safer, from the point of view of rheumatic infection, to live in overcrowded rooms than in the more chilly respectability of a jerry-built villa. In areas of equal poverty I do not doubt that the damper area would show the heavier incidence of rheumatism, but I also think that owing to excessive damp, a respectable working-class area may show more rheumatism than a drier slum.

Hæmolytic streptococcal infections.—I am not sure as to the position which the question of hæmolytic streptococcal infections occupies at the moment in the epidemiological arguments. When the early papers on this subject appeared, it seemed that an attempt was being made to prove that the actual bacteriological cause of rheumatism was a hæmolytic, rather than—as we believe—a non-hæmolytic streptococcus. On the other hand, such infections may be regarded merely as precursors of true rheumatic infection. There is all the difference in the world in the significance of the two views. If it were proved that the causative agent of juvenile rheumatism is a hæmolytic streptococcus, there would be need for a considerable re-arrangement of our ideas, but much stronger evidence than has yet been brought forward would be needed to establish this view, and I must confess to being surprised that it is suggested that serum and skin reactions are of value in typing streptococcal infections.

On the other hand, if hæmolytic infections are merely exciting factors, it seems as though this view was only expressing in bacteriological language what has long been known clinically, namely, that epidemic sore throats will activate rheumatism. Although perhaps the association is closer, there seems no essential difference here between the action of hæmolytic infections and the known action of such infections as scarlatina, diphtheria, and, sometimes, other infectious diseases.

Allergy.—I cordially agree with what W. Sheldon has written, that if we knew what is happening in the interval between the throat infection and the occurrence of systemic rheumatism, much of importance in the pathogenesis of carditis would be revealed. Although the occurrence of such a silent interval is a very old observation, too much must not be made of it, as it is quite frequently absent. But it is in connexion with this latent period that one rather longs to be able to accept some explanation involving allergic reaction, as has been suggested by Schlesinger, Macdonald and others. But can we? Is it possible that allergy can account for one infection paving the way, as it were, for another; or can allergy have any action

in determining the onset of an infection of the blood-stream? Until these things are shown to be within the range of allergic phenomena, we must be content with our present position.

Contagion.—The question of contagion as a means of the mass-production of juvenile rheumatism is becoming rather complicated. Put in its baldest form that the disease is communicated from one case to another, and hence the necessity of proving the importance of overcrowding as a factor, it is, I think, unacceptable. We know in our bones that it is not true. Or again, if the hæmolytic streptococcus of epidemic sore throat is to be regarded as the actual causative agent of rheumatism, thus making rheumatism a contagious disease, we still cannot agree as we do not admit the facts.

There is, however, a third proposition, namely, that an infectious sore throat may set up juvenile rheumatism, although the one is due to a hæmolytic, and the other to a non-hæmolytic, streptococcus. This may readily be admitted. It has long been known that epidemic sore throat, which is usually associated with hæmolytic streptococcal infections, can at least unmask or reactivate rheumatism, though it is not so certain that it can originate the disease. From the analogy of scarlatinal infection it is probable that it can do so. The study of outbreaks of epidemic sore throat followed by outbreaks of rheumatism merely brings into greater prominence the activity of the hæmolytic infections as exciting factors in rheumatic attacks; but all this does not prove rheumatism to be a communicable disease.

Can we go further? Can we hold that, apart from outbreaks of rheumatism secondary to outbreaks of epidemic sore throat, the ordinary seemingly sporadic case of juvenile rheumatism is set up by latent or accumulating infection by hæmolytic streptococci. If this were proved, although, strictly speaking, it would not make rheumatism a contagious disease, it would be a consideration of the utmost importance. There is nothing in our knowledge of juvenile rheumatism which precludes such a possibility. Indeed, in some minor ways there are suggestive points in its favour, but I must remind Dr. Glover that a good many of us have searched the throats and fæces of rheumatic children for evidence in favour of this view and have failed to find it. Evidence from exceptional outbreaks of rheumatism does not weigh with us: the analogy between epidemics of catarrhal throats and scarlatina is too close. But evidence in the ordinary individual cases of juvenile rheumatism would be altogether another matter.

To sum up: The British Medical Association report seems to me to have been correct when it said that juvenile rheumatism was essentially a disease of children of the artizan class, living in damp houses in an industrial town, attending an elementary school under compulsion, and suffering from infected tonsils. It seems to me still true that, although these environmental factors, taken together, are of such importance that they determine the incidence of rheumatism, yet even now no single factor taken alone appears to have an overwhelming influence.

Dr. W. S. C. Copeman: The importance of secondary factors lies in their power of influencing the course of the disease. This they may do (i) by influencing the infecting germ, or (ii) by modifying the resistance of the body. There would appear to be no reasonable doubt that, clinically, rheumatism is influenced by *climatic factors*, although observations on this point with relation to chorea seem to be lacking. Some very interesting charts have been drawn up by W. Sheldon from a series of cases, in which the correlation between weather conditions (rain) and the rheumatic pains experienced by children in a London hospital was shown to be very intimate. This work was based on the weekly study of 100 child out-patients. In the early part of the year 1929, the number of children complaining of pains was

high, although the rainfall was low, but afterwards the rainfall curve was followed very closely, even to an exceptionally high peak, in July. Again, during the drought in September, no children complained of pains. More observations of this sort are needed. It is commonly believed that barometric variations are in themselves able to cause rheumatic recurrences. It is, however, difficult to find proof of this, whilst the meteorological delegates to a recent congress on this subject definitely denied such a possibility.

The question of soil and that of dampness are, at any rate in rural districts, inseparable, since a non-porous subsoil, where the ground is not on a steep slope, inevitably means that the air above it will contain a high percentage of moisture. It also appears that the question of temperature variations is almost equally dependent on these two factors since, in a recent paper by Captain Brunt of the Air Ministry, it was shown that soil containing 20% of moisture returned only one-fifth of the radiation which dry soil was capable of returning. This means that in damp localities the temperature variations in the twenty-four hours are very considerably less marked than is the case in those well-drained dry localities which are apparently more suitable for the rheumatic patient.

These observations are contrary to the general lay belief, but confirm my view of the necessity for the conjunction of damp and cold in the unmasking of these cases. Mere variations in temperature do not seem to be of great importance, nor does the presence of damp alone when the other circumstances (good food, clothing, etc.) are favourable. This was convincingly shown by Newman in the report of his investigations into the reason for the absence of acute rheumatism at the Fountain Hospital, where, amongst other adverse factors, there was a cellar under his ward which was flooded, if not pumped out, even in summer! This fact may explain the different opinions held by good observers on the subject of the topographical distribution of cases occurring in cities.

It would seem that so far as dampness is of itself a factor to be reckoned with ætiologically, it is the dampness of the person rather than the dampness of the place which is of importance. We should otherwise expect Eton College, which is very low-lying, to head the school rheumatic statistics in this country. It is where we get damp in conjunction with chill that rheumatism appears to flourish, presumably owing to the resultant depression of the individual resistance to disease via the heat-regulating mechanism of the skin. The rheumatic child is unable to adapt the response of his skin to the demands of his environment. This has been shown in scientific form by the investigation of skin surface temperatures in these cases by Van Breeman and others.

With reference to the question of climate, it has often been pointed out that geographically the disease is almost exclusively one of temperate and subtropical zones, the arctic regions equally with the equatorial regions being immune. It must be remembered, however, that we are exposed to natural climate for at most only one-third of our lives; for the rest we live in an artificial "micro-climate" of our own choosing, which lies between our skin and our clothes, or bed-clothes. It is in this "climate" that the conjunction of cold and dampness is found most commonly in children who, as the result of poverty, are underfed and improperly clothed.

To eliminate moisture from this "micro-climate" immediately surrounding the skin, the clothing must be porous and non-hygroscopic, but at the same time must be a poor conductor of heat (heat retaining). Much can, I feel sure, be done for these children by advising parents on the question of adequate clothing material. With regard to bed-clothes, it is commonly recognized that rheumatic children are best nursed between blankets, rather than sheets, which are more porous and of greater heat conductivity. Wool, or one of the new cellular materials, is for the same

reason, best for wearing next to the skin. Flannel, although a bad conductor of heat, does not allow of adequate evaporation of moisture.

It has been suggested that the rheumatic "diathesis"—a term beloved by the older physicians, but now covered by the term "rheumatic predisposition"—consists essentially in a failure of the power of the skin to adapt itself to its surroundings, so permitting "chill" and a lowering of resistance. It has also been suggested that such a failure may be quantitative rather than qualitative. Such an alternative might be found in cases where this mechanism would function, but only between narrow limits, the limits of adaptation being more easily exceeded than normal.

Where a disease group tends to show a "class-consciousness," as in the case of acute rheumatism, it will often be found that a diatetic factor is to some extent operative. This may merely prove to be a question of defective calorie production, or may, as Warner believes, go deeper ætiologically.

With regard to overcrowding as a separate factor, it is difficult to see exactly how this can be operative. It is, however, practically invariable below a certain poverty level, and is probably only an associated factor.

In conclusion, it is suggested that in acute rheumatism :—

(1) Secondary ætiological factors should be accorded the same attention as those believed to be primary.

(2) These factors lie in the province of clinical research and observation, in which field most competent physicians can engage. It is believed widely that this field has been "played out." This can, however, scarcely be true, in view of the fundamental uncertainty prevailing at present.

(3) The rheumatic diathesis consists essentially in the failure on the part of the skin of these patients to adapt itself to changes in their climatological environment, so permitting chill and a lowering of body resistance, and that it is on the basis of this abnormality that climatological factors produce their effect.

(4) The climatological factors responsible for determining the onset of rheumatism are a conjunction of cold and damp in the "micro-climate" of the individual.

(5) A dietetic factor is, in all probability, also operative in many cases, but is of less importance than the foregoing.

Dr. E. C. Warner: I wish specially to call attention to the possibility of a biochemical and dietetic factor, which may predispose to juvenile rheumatic disease. The view that I am putting before you is purposely rather overstated, in order to give prominence to it.

I am going to suggest that some of the manifestations of juvenile rheumatism may not be of infective origin at all. No one will deny that the carditis is a manifestation of infection, but we must not therefore assume that all rheumatic manifestations are of infective origin. I suggest that it is not proven that uncomplicated chorea and even the pains of subacute rheumatism and the joint swellings of acute rheumatism are due to an infection. I shall develop this thesis in the case of chorea. In chorea uncomplicated by carditis we find no rise of temperature, no tachycardia (allowing for the slight rise due to the movements themselves), and also no change in the leucocyte count. Any rise of temperature is a warning of the onset of carditis. Recently we have studied a still more delicate test of infectivity, in the sedimentation rate of the blood. In almost every disease that is due to an infection there is an increase in the sedimentation rate, and the only disease that I know of which does not conform to this rule, is chronic leprosy. In uncomplicated chorea there is no increase, yet as soon as carditis sets in, and even before it is manifested clinically,

there is a tremendous rise in the sedimentation rate. This is well illustrated in the table below.

SEDIMENTATION RATES IN CASES OF CHOREA.

		1 hour	2 hours
Jean H. ...	Moderate chorea. Heart and temperature normal. Gaining weight well	6 mm.	12 mm.
Ethel W. ...	Mild chorea. Heart and temperature normal and gaining weight well	3 mm.	6 mm.
Stella S. ...	Mild chorea. Heart and temperature normal and gaining weight	7 mm.	16 mm.
,, ...	Chorea practically gone. Heart normal	7 mm.	21 mm.
Vera McC.	Mild chorea. Heart and temperature normal, not gaining weight	10 mm.	18 mm.
Pat H. ...	Moderate chorea. Heart normal...	3 mm.	6 mm.
,,	Five weeks later no chorea, but shortly afterwards carditis with a relapse of chorea and temperature of 100° developed	51 mm.	60 mm.
Leonard A.	Moderate chorea. Heart apparently normal. Later an indistinct first sound at apex	15 mm.	31 mm.
,,	Chorea less. Still muffled first sound at apex	12 mm.	23 mm.

These findings have recently been confirmed by Dr. A. Polak Daniels, Amsterdam.

If chorea is an infective disease, why do we not get an increase in the sedimentation rate until carditis supervenes? Then again, in a number of cases of chorea, the most careful section of the brain at autopsy may reveal no inflammatory reaction, as was demonstrated again recently by Dr. Bernard Shaw. Another point that was made originally by Dr. Leonard Findlay, was that if a child has had three attacks of chorea without developing carditis, he may have any number of subsequent attacks of chorea without the danger of carditis. Still another point which I think demonstrates the biochemical side is obtained by studying the muscle reactions and the calcium and phosphorus readings in cases of chorea. In the *Proceedings* of the Section of Therapeutics, in 1932 [1] are published results obtained in chorea, showing how the neuromuscular excitability lessens as the chorea subsides. Studies of the calcium and phosphorus contents of the cerebrospinal fluid were then made, as in the cerebrospinal fluid these substances are all in an inorganic (and therefore active) state, and none are in combination with protein as in the blood. In the acute stages of chorea the cerebrospinal fluid calcium is low and the phosphorus high, and as recovery ensues the calcium rises and the phosphorus falls to reach the normal values. Recently Dr. Gray-Hill and I have found in a small number of cases that those in which the blood calcium rises most rapidly appear to be those which make the quickest recovery.

Similarly in subacute rheumatism, and even in acute rheumatism, I do not think it is proven that the muscle pains and joint pains are due to an infection. Similar muscle pains occur in acute fibrositis as a result of chill, and on two or three occasions I have seen cases of children who have had undeniable rheumatic disease in the past, and who have appeared with one or two joints swollen and warmer than normal, in which there has been no history of trauma, and no pyrexia or other rheumatic manifestations. Surely if this acute joint swelling is due to an infective arthritis, we should expect more constitutional disturbance. Still one more point arises: It has been urged by many different workers, and by C. W. Vining in particular, that before the acute outbreak of rheumatic disease there is a long period of debility, with various symptoms, such as pallor, sweating, loss of weight, etc., for weeks or months beforehand. Does not this argue in favour of an underlying biochemical state which predisposes to an infection? In juvenile rheumatism we may be dealing with a disease comparable in many respects to diabetes mellitus: here an underlying metabolic condition may give rise to a variety of symptoms such as coma, neuritis, arteriosclerosis which are all due to the metabolic disturbance, but where an infection such as tuberculosis may readily arise. In this case no one would argue that because tuberculosis commonly occurs with diabetes, therefore the

[1] *Proceedings*, 1932, xxv, 1213 (Sect. Therap., 19).

diabetes is due to a tuberculous infection. Similarly here we should broaden our vision and not jump to the conclusion that because carditis commonly occurs in juvenile rheumatism, therefore all the symptoms and varieties of rheumatism are due to an infection.

Arguing along these lines, I have endeavoured to find whether there is a dietetic deficiency or imbalance contributing to the predisposition to juvenile rheumatism, and possibly explaining the results of the calcium and phosphorus studies already recorded in chorea. There are many *a priori* reasons for thinking that such may be the case. I have already mentioned the long period of debility which often precedes the initial attack or relapse of manifest rheumatism, and the child who is particularly prone to a relapse is the child who is becoming below par and is not gaining weight satisfactorily. Also, as Dr. Glover has told us, rheumatism is a poverty disease, and I agree that it is the poorest who are most commonly attacked. Yet when we take these same children and put them in better hygienic conditions in residential schools, and accompany this change by better feeding, the incidence of rheumatism lessens enormously. I am not denying the value of the better care, fresh air, and housing that this involves, but when we examine the dietaries we find what a great improvement has been effected in this direction also. The strikingly low incidence of rheumatic fever in the Great War, in spite of appalling hardships and damp conditions generally, may well be related to the good feeding among the troops. May not the familial incidence and also the special occurrence in the winter and spring months all be related to a familial dietetic factor and a deficiency of food in the hardest months of the year?

Dr. Winterton and I have been making a particular study of these problems, and our results will shortly be published. The rheumatic families showed no lack of total calories as the average intake, working on Cathcart's man-value basis, was 3,261 calories per man per day. Neither was there any lack of protein, with a value of 96·5 grm. per day, or of animal protein. But compared with the better-class family diets, the carbohydrate intake was excessive and the fat intake only two-thirds of the better classes as recorded in the St. Andrew's study. From a comparison of the likes and dislikes of the rheumatic children with those of their non-rheumatic brothers and sisters, and with those of control children, the appetite of the rheumatic children was rather less, and they were less fond of milk and butter, but rather more fond of potatoes. This was corroborated by a study of the actual food consumption of a group of rheumatic children and of control children. On the man-value basis the milk and butter consumption of the rheumatic children was 0·496 pints and 0·048 lb. per day as compared with 0·516 pints and 0·061 lb. per day in the controls. Whereas the rheumatic children consumed 0·741 lb. of potatoes, the control figure was 0·617 lb. per day. But perhaps the most striking confirmation of this view was from data kindly supplied by Dr. Friend, from Christ's Hospital. As the diet of the boys was improved by the addition of more animal fat and the elimination of some of the starches, the incidence of rheumatism fell from 19 in the first period of five years, to six in the third period.

To sum up this evidence: I suggest that many of the manifestations of juvenile rheumatism may not be of bacterial origin, but are of metabolic origin; until we know the causal organism we should broaden our view and realize that we may long have overstressed the bacterial factor, and it may be that the future will show that one of the best ways of removing the scourge from our midst is to raise the general resistance of the patients by a better balanced diet. The value of extra animal fat and milk in reducing the tendency to catarrhal attacks is well known, and was beautifully demonstrated by Corry Mann in his report published in 1926; and the evidence we have adduced in our study of rheumatic children makes us believe that this may be of equal importance in overcoming the "rheumatic diathesis."

Dr. R. L. J. Llewellyn: That environmental factors enter largely into our ætiologic concepts of "rheumatism" is undeniable, since upon the human organism are incessantly impinging multiple physical stimuli—heat rays, light rays, ultra-violet energies and changes in temperature, humidity and barometric pressure, to all of which "cosmic" or environmental forces the organism must swiftly and adequately adapt itself or fall a prey to disease. For individual adaptive capacity is Nature's "acid" test for weeding out the fit from the unfit.

Recently Bassett Jones and I discussed the fundamental fact in relation to "rheumatism" that man and his environment are one and indivisible, affirmed our belief that ultimately rheumatism would be regarded as primarily a disorder of the skin and only secondarily of the joints, muscles and other structures. Now the organism achieves contact with, and adaptation to, "cosmic" forces through the sympathetic and parasympathetic divisions of the endocrine-autonomic system. If this intermediary mechanism reacts normally, the organism harmonizes with its environment; if otherwise, comes in conflict therewith. In these multiple adaptive processes the cutaneous glands play an important rôle, notably the sweat-glands in temperature stabilization, but there are indications that the *sebaceous* glands also participate in this vital process. Except on hairless regions, the sebaceous glands are almost as widespread as the sweat-glands; their salient feature being their absence from palms, soles and dorsal aspect of terminal phalanges. The sebum moistens the epidermis and lubricates the hair. Moreover these glands, being numerous and closely aggregated, the sebum exuding from their ducts spreads over on to the surrounding skin and so keeps it supple, resilient and waterproof. That the skin is pierced by ducts is not incompatible with its waterproof consistency as a whole. Again, this skin coating with sebum rendering it impervious to water prevents desiccation of underlying tissues through excessive loss of moisture. Also but for this action of sebum on the skin, immersion of the same in water would induce swelling of the subjacent tissues through imbibition. Finally, as to its influence on temperature stabilization, the admixture of sebum with sweat retards the rate of evaporation of the latter. In short, unlike sweat which promotes heat-loss, sebum favours heat-retention or conservation.

Clinically it is significant that during infancy and childhood the sebaceous glands are relatively inactive. Hence the skin, as a whole, suffers from lack or insufficiency of sebum, which in turn spells lowered resistance of the skin surface to damp or humidity. Again, palms and soles being destitute of sebaceous glands and their correlated sebum are especially sensitive to damp or humidity and such may in part account for the liability of rheumatic children to so-called "growing-pains." But the years of incidence of growing-pains coincide with those of the natural growth process referable to the anterior pituitary hormone and vitamin A, which latter is as essential for general, as vitamin D is for bony or skeletal growth. Can lack of deficiency of vitamin A account for the painful character of so-called growing pains?

Discussing the odour of the sweat in acute rheumatism in childhood, that astute clinician, Goodhart, said, "of acidity of smell there is no trace." Can it be doubted that this is due to the relative inactivity of the sebaceous glands at this period? For the evil odour of the sweat in acute rheumatism after puberty is notorious and strikingly contrasts with that of acute rheumatism prior thereto. Obviously children, especially if of rheumatic stock, are sorely crippled by deficiency of sebum in their skin which undermines their defence against damp or humidity, also by diminishing their capacity of heat retention promotes temperature "instability" and lowered or subnormal temperature. Moreover, sweat lacking due admixture with sebum evaporates swiftly, with "chilling" of skin surface, either general or local, whence the liability of children either to cutaneous or pulmonary disorders or to local rheumatic affections, e.g. stiff neck, and so on.

Nor do the foregoing exhaust the disabilities resulting from diminished sebum content of the skin during infancy and childhood. For the chief chemical constituent thereof is cholesterol whose invariable concomitant is ergosterol. The latter, under the influence of sunlight, or of ultra-violet rays of certain wave-lengths, is synthesized in the skin into the anti-rachitic vitamin D. The skin being a veritable depot of cholesterol, I have long surmised that, apart from ergosterol, animal cholesterol—a mixture of sterols—endows the skin with the quality of photosensitiveness. In the later months of pregnancy the blood-content of cholesterol increases considerably and after delivery the excess of cholesterol is excreted in the maternal milk. Hence, suckling increases the low cholesterol content of the infant's blood, enhancing its sensitiveness to light and so prevents the possible development of rickets and perhaps rheumatism. For these two diseases are not mutually exclusive, the age incidence of rickets and infantile acute rheumatism sometimes overlapping. McCrae and Osler have recorded 10 cases of undoubted acute rheumatism in sucklings. It is, I think, the heredity factor which decides whether the infant shall escape the Scylla of rickets only to be engulfed by the Charybdis of acute rheumatism. The point I would emphasize is that absence or deficiency of sunlight, or of ultra-violet rays, is as vitally concerned in the genesis of rheumatism as it is in that of rickets.

Essenger and Gyorgy find that after ultra-violet irradiation the blood-content of cholesterol increases and simultaneously—so other authorities claim—also its content of the amino-acids, tyrosine and cystine. Thyroxin and adrenalin are chemical derivatives of tyrosine which, in union with cystine, begets insulin. These three hormones are responsible for heat production, always deficient in infants and children, especially those of rheumatic heritage. Hence I hold that the basal physiological flaw in rheumatism is an inborn tendency to thermal instability, this same being due to deficient storage in the epidermis of tyrosine and cystine, which may be absolute or relative, the outcome of inadequate exposure to sunlight or ultra-violet rays. How abject then the plight, physiologically, of the child or infant, victimized from birth or even prenatally by deficient storage of tyrosine and cystine in its epidermis plus inadequate exposure to sunlight or ultra-violet rays. Such connotes not only diminished transference of tyrosine and cystine from the epidermis into the blood, but potentially lessened formation therein of thyroxin, adrenalin and insulin. Hence an infant or child crippled by these cutaneous disabilities and still more by their remote physiological consequences will, *ipso facto*, find it difficult, if not impossible, to stabilize its body temperature, and this is precisely what the potential or actual rheumatic child cannot achieve. Still more deplorable is his condition if to this be superadded the relative deficiency of sebaceous secretion incidental to infancy and childhood, since this spells inadequate storage of cholesterol, and therefore of ergosterol, in his epidermis and consequently diminished response to the great "cosmic" factor, sunlight or ultra-violet rays.

Moreover, if, as Essenger and Gyorgy claim, the blood content of cholesterol increases after ultra-violet irradiation, a further question arises. Animal cholesterol, being invariably correlated with ergosterol, the same may be regarded as a vehicle for the latter. This being so, may not animal cholesterol, in virtue of its ergosterol content, act as a medium for the transport of light or ultra-violet energies into the blood-stream, since some believe that light energies taken up by the skin are absorbed by the superficial capillaries, stored, and carried to the various parts of the body, stimulating intracellular oxidation and reduction processes in the tissues. This suggested possibility is very germane to rheumatism in childhood, for clinically there is much evidence that in these children the oxidative faculty is deficient. Adequate, perhaps, in an equable climate, but not in our variable climate, whose sudden changes transcend their feeble powers of adaptation, since the processes of tissue oxygenation are exquisitely conditioned by cosmic or physical forces incessantly in operation.

Again, what of the excess of those light-sensitive bodies, the porphyrins, excreted in acute rheumatism, as Gideon Wells observes in his work on chemical pathology. Do not hæmatin and its related pigments belong to the porphyrin group? Hæmatin, too, is an iron porphyrin. Warburg's researches indicate that some similar, if not identical, substance is deeply involved in cell-oxidation. Wright claims that the spectroscopic evidence that the respiratory enzyme is related to hæmatin is decisive. May not excessive leakage of porphyrins account for diminished tissue oxidation in acute rheumatism?

In conclusion, as is well known, in widespread rickets, exposure to ultra-violet rays of one joint or limb alone suffices to cure even remote rachitic lesions. This would be inexplicable except on the assumption that the visible and the long—if not the short—ultra-violet rays penetrate deeply enough to influence the blood in the superficial capillaries of the dermis. If this be so, a fascinating vista of the possible depth and range of action of ultra-violet radiation is thus opened up. Considering also the essential rôle played therein by cholesterol and its correlate ergosterol, I have, I trust, justified my plea that, as in rickets, so also in the rheumatism of childhood, should increasing attention be devoted to the study of the sebaceous secretion and its contained sterols.

Dr. Bruce Perry said he agreed with Dr. Miller that it was difficult to accept the theory that acute rheumatism was an allergic reaction to the hæmolytic streptococcus. Collis had definitely shown that in some cases erythema nodosum was a manifestation of hypersensitivity to the endotoxin of the hæmolytic streptococcus, and most clinicians would agree that erythema nodosum was rarely associated with rheumatic carditis—the hall-mark of acute rheumatism. Personal observations on the sedimentation-rate in chorea uncomplicated by carditis paralleled Dr. Warner's findings that in such cases the sedimentation-rate was normal, but rose rapidly with the onset of carditis, the rise in the sedimentation-rate sometimes preceding the clinical recognition of carditis. The Bristol and Three Counties investigation had shown one striking positive fact which was that the incidence of fresh cases of rheumatic heart disease during the three-year period studied was very considerably higher in Bristol than in the surrounding counties. A closer study of the Bristol cases showed that there were even greater differences in the distribution of the disease in the various municipal wards of the city, than between the city and the counties. The incidence varying from 3·7 per 1,000 of the population to 0·15 per 1,000. It was thought that, if the concentration of hæmolytic streptococci played an important part in this variation, the incidence of scarlet fever over the same period should parallel that of rheumatism. This, however, was far from the case; the incidence of scarlatina was fairly uniform all over the city, varying in the different wards from 11·9 per 1,000 to 5·9 per 1,000. Diphtheria, a disease with no relationship to acute rheumatism, yet with a similar mode of infection to that of scarlet fever, had also been investigated. There were rather larger variations in the incidence of this disease, which varied from 13·8 per 1,000 to 3·1 per 1,000, but these differences were nothing like so marked as in the case of acute rheumatic carditis.

With Dr. Herapath, a study of the distribution of the cases of rheumatic heart disease in the various elementary schools had been made. In one school an epidemic of scarlet fever had led to six cases of rheumatic carditis from July to December 1927. No other example of anything that could be considered an epidemic had been found. The variations in the incidence of rheumatic carditis in the municipal wards closely followed the degree of overcrowding, but the latter was in no way associated with the incidence of scarlatina or of diphtheria. These findings suggested that the high incidence of rheumatic carditis in Bristol was due, not so much to a concentration

of the infecting agent (if that was the hæmolytic streptococcus), as to the conditions under which the children lived.

Professor J. A. Nixon : It has already been observed that the incidence of acute rheumatism is much lower in Poor-Law residential schools than it is amongst children of the same social class attending public day schools. Also it is almost entirely absent from the great public boarding schools, although this immunity occasionally appears to break down. Recently one of the medical officers at a school of the latter type told me that whereas for twenty years no case of acute rheumatism had occurred, there had been four or five cases during the last ten years.

I desire here to call attention to another form of closed community from which acute rheumatism is absent. I refer to two institutions for mental defectives in Bristol, a city which has a notoriously high general incidence of acute rheumatism. At Southmead Hospital there were, for some ten years, from 100 to 150 mentally defective children. During that time no first attack of acute rheumatism was recorded amongst the inmates of this section of the hospital. Yet the son of the superintendent developed severe nodular rheumatism with cardiac involvement. The climate and residence were the same for this child as for the others. It is unlikely that he was worse fed or clothed than they were. The only difference that I can suggest is that he attended a day school at some distance from the hospital.

At Stoke Park Colony Dr. R. Bates, the resident medical officer, has furnished me with some interesting figures. During the two years 1932 and 1933 the total number of inmates was 1,850. The average daily population was about 1,540, and the number of new admissions was 287. These admissions were nearly all children of school age. No first attack of acute rheumatism was seen in the whole colony, yet there are many inmates with histories and cardiac evidences of previous rheumatism. There have been several epidemics of scarlet fever and of respiratory disease due to hæmolytic streptococci during that period. My own experience is that mentally defective children are particularly liable to streptococcal sore throats and to pulmonary infections with streptococci. We have proof at Stoke Park that the children have not shown any remarkable immunity to acute rheumatism before their admission and yet after they enter the institution they appear to escape. I venture to suggest that thorough investigations of communities that are "rheumatism-free" are necessary. This was Jenner's method with smallpox, and it was the method which Goldberger employed in his studies of pellagra ; in the institutions that he visited he persistently inquired as to which patients escaped and presently he gave the explanation of their escape.

Dr. Fortescue Fox said he recalled the fact that at the beginning of his career, fifty years ago, when he was house-physician at the London Hospital, there were constantly admitted to the wards a considerable number of cases of typhoid fever and of rheumatic fever ; often these diseases were side by side, and it was an extraordinary interest for him at that time to watch the evolution of these acute diseases, although in more recent years he had been concerned with the problems of chronic disease.

Dr. Leonard Findlay said that he had really come to this meeting to learn, but perhaps, as one of the members of the Child Life Committee of the Medical Research Council, and being responsible for the part of the investigation carried out in Glasgow, he had some little claim to speak. When Dr. Glover said he intended recording the progress made since the publication of that report he, the speaker, was hopeful that we were going to learn something of a real step forwards, but he must say that he was disappointed.

It was generally believed, and he thought rightly so, that the disease was of the nature of an infection, and hence it would be remarkable if it were not influenced by social conditions, either by favouring the transmission of the infective agent, or by undermining the health of the individual and rendering him more susceptible. Dr. Warner's objections to the disease being infectious were, to the speaker's mind, hardly tenable. A leucocytosis was not necessary in an infectious process; enteric fever was an example of an infection in which a diminution of the number of leucocytes was the rule. Nor was it necessary to have fever, since in influenza, another infection unaccompanied by leucocytosis, a complete absence of fever was not infrequent.

While listening to the discussion one could not but recall the work of Dr. Alison Glover during the War in connexion with cerebrospinal fever, and how he had brought order out of chaos by revealing the explanation of the environmental conditions under which this disease developed. But in cerebrospinal fever the specific cause of the disease was known. In the case of the rheumatic infection, on the other hand, we did not really know the specific ætiological organism. Like Dr. Miller he did not believe that it had been established that the hæmolytic streptococcus was the ætiological factor. The bacteriological and the serological findings of the various workers throughout the world were far too varied, and the disease was too constant in its manifestations for him to believe that the hæmolytic streptococcus was the cause. In this connexion he drew the attention of his audience to the original paper on the question by Drs. Poynton and Pain, in which illustrations of the vegetations on the valves showed these literally teeming with cocci. Surely, if these revealed the true state of matters, there would be no difficulty in seeing the organisms and there would be greater unanimity in the findings.

There must be some other factor. Was it a question of symbiosis or was it a question of environment? Was it that the real causal organism only flourished in the presence of the streptococcus or under certain environmental conditions? It had been known for long that any infection was liable to set up or light up an attack of rheumatic fever, and certainly the latter frequently followed a sore throat and the infectious diseases, scarlet fever and diphtheria. His interpretation of these factors was that the door, or one of the doors, was opened to the infection, whatever its nature might be.

He must admit that he had a difficulty in correlating Dr. Glover's enthusiasm this evening for the streptococcus, and for acute throat conditions, in seeking a cause for the disease, with the views which he had frequently expressed regarding the futility of tonsillectomy in controlling or having any effect on its incidence; indeed, according to him, removal of this portal of entry rather increased the incidence of the disease. However, in his summing up, Dr. Glover had to return to the importance of environmental conditions and his conclusions were essentially those come to by the Medical Research Council Child Life Committee.

Dr. Warner wished to raise the question of diet as being a contributory factor. It was regrettable that he had selected chorea as the condition for the study of this factor since chorea was of all the manifestations of the rheumatic infection the least characteristic and invariable. He made the same criticism of Dr. Warner's remarks on the infective nature of the disease. It was also a pity that Dr. Warner, in the tables referring to the different dietetic factors, only gave average figures and made no reference to the maximum and minimum, so that the important point of overlap was not considered. To-night, however, so many environmental factors had been given significance that there seemed a danger of not being able "to see the wood for the trees." Nevertheless, we did know that rheumatic fever was absent from the children of the class which was most subject to it, when they were transferred to satisfactory housing conditions: thus, though the true cause had not yet been

found, the disease could be largely prevented by seeing that the poorer classes had decent houses to live in.

Dr. E. W. Goodall said he wished to ask Dr. Glover whether the institutional rheumatism had followed an attack of tonsillitis or not? If there had been tonsillitis, should not the rheumatism be looked upon as a complication of the tonsillitis? If so, one would not expect acute rheumatism, as such, to be infectious from one person to another. In the case of diphtheria, for instance, a common complication was paralysis, but if paralysis was present in a diphtheria ward, the paralysis was not transmitted from one patient to another.

Dr. Gray Hill said that the fact that children living in residential schools and other institutions so seldom developed rheumatism pointed to there being a definite environmental factor in the disease. What exactly the difference between the environment of the home and that of the institution was, it was hard to say. He, himself, had been impressed by the fact that at the hospital at Carshalton the acute manifestations of rheumatism were very seldom seen. Since 1926 over 3,000 rheumatic cases had been admitted to the hospital. They had all had active signs before admission, and a certain number relapsed after discharge, yet during their stay in hospital, a period usually from three to nine months, active manifestations, with the exception of chorea, were very rare. Most of the children did well, and there was a marked improvement in their general health. He did not think that climate or locality could be the real factor; the change from London was not great enough. Also the children did well when sent to a small seaside home at Littlehampton, where the conditions were very different from the chalk downs of Surrey, where the hospital at Carshalton was situated.

It would almost seem that an environment different from that of their own homes was beneficial to rheumatic children.

Dr. Alison Glover (in reply to Dr. Goodall) said that nearly all the cases of rheumatism to which he (the speaker) had referred had had an initial tonsillitis.

Dr. Findlay had suggested that almost any infectious disease might activate acute rheumatism; with that statement he could not agree, as he thought that infection by a hæmolytic streptococcus was necessary. He agreed that diphtheria might be followed by acute rheumatism, but it was not uncommon to find that many patients with diphtheria had a secondary or concurrent infection with hæmolytic streptococci.

Judging both from Professor Nixon's experience and from the careful investigation by Dr. J. L. Newman, to which both Dr. Copeman and he (the speaker) had referred, it would seem that mental defectives tended to have a low incidence of acute rheumatism.

Dr. R. Miller (in reply), referring to Dr. Warner's paper, said that it was doubtless true that most cases of chorea were due not to an infection of the brain but to a toxæmia, and their temperature charts showed the typical evening rises of toxæmia although the temperature might be subnormal throughout. Also it was probable that choreic symptoms might remain for some time after active infection had subsided. To turn aside from the admitted relationship between rheumatic infection and chorea and invoke minute changes in the intake of various articles of diet, seemed to him a serious step for Dr. Warner to take. He thanked Dr. Findlay for so boldly stressing the housing factor in the production of juvenile

rheumatism. He also agreed with his view that there was still some ætiological factor missing to explain the production of the disease. He felt confident that this was not a food factor, but whether it was an allergic factor or was due to the carrier-rate of hæmolytic streptococci, it was important that we should realize that there was some factor still eluding us, and that juvenile rheumatism was not the mere result of a fortuitous meeting between a germ and a child.

JOINT DISCUSSION No. 4

Section of Orthopædics and Section of Surgery

Chairman—GEORGE E. GASK, C.M.G. (President of the Section of Surgery)

AT A MEETING HELD AT THE ROYAL COLLEGE OF SURGEONS, FEBRUARY 6, 1934

DISCUSSION ON FIBROCYSTIC DISEASE OF BONE

Mr. R. C. Elmslie: The name "osteitis fibrosa" has been applied to a miscellaneous group of cases of bone disease, in which the skeleton shows some or all of a certain group of pathological changes. These changes are:—

(1) Lacunar absorption of bone by osteoclasts, either locally in one place, or in several localities, or generally throughout the skeleton.

(2) Deposit of new bone of an irregular texture (woven bone).

(3) Fibrosis of the marrow, which, again, may be local or general, and which may simply mean that the marrow contains more fibrous tissue than normal, or may mean that it is entirely replaced by masses of fibrous tissue.

(4) The formation of cysts. These may lie in the bone, with only a bony wall, or there may be a fibrous lining, or the cysts may lie in the masses of fibrous tissue.

(5) The formation of osteoclastomata, i.e. giant-celled tumours, such as were formerly called myeloid sarcomata. They may be single or multiple.

(6) Sometimes, the development of cartilage.

We must recognize that these are changes which may occur in the bone from varying causes; none of them is peculiar to any one disease. It is unfortunate, therefore, to find pathologists reporting on the histology of a specimen of bone as showing "the changes of osteitis fibrosa cystica." Even if the clinical and pathological picture leads him to arrive at this diagnosis, he should give a detailed report upon the changes shown in every case.

Since Virchow's first description of a bone-cyst in 1876 and Von Recklinghausen's description of the generalized disease in 1891, an extensive literature has arisen, and a whole medley of cases of different varieties has been recorded, so that it is by no means simple to sort out the cases. Nevertheless I believe that it is possible to make a series of clinical or clinico-pathological pictures classing the cases in groups and giving them definite names.

I would classify the cases into the following groups:—

(1) *The bone-cyst.*—This is formed by lacunar absorption of bone by osteoclasts. It contains brown fluid, and is often surrounded by bone which shows lacunar absorption and has no lining membrane. Sometimes, however, it has some soft cellular tissue at its margins; sometimes it has a membranous lining. In the latter

case I suspect that it has been the seat of a recent hæmorrhage. Occasionally cartilage has been formed in the bone around the cyst.

These cysts may occur in almost any situation, but are particularly frequent in the upper end of the humerus and of the femur.

(2) *Osteoclastomata.*—These are the classical myeloid sarcomata. They need no further description, but they must be included because of their relationship to cysts, as shown by the next group, and because of their occurrence in cases of hyperparathyroidism.

An osteoclastoma can be cured by curetting, but after the curetting the cavity may fail to clear up and a bone cyst may thus be left.

I cannot leave the subject of osteoclastoma without referring to the xanthoma—a remarkable tumour, bright yellow in colour, growing in the interior of bone. Histologically it is characterized by the presence of polyhedral cells with small nuclei containing granules.

It is recognized that this tumour is related to the osteoclastomata, and this relationship is illustrated by a case of xanthoma of the lower end of the tibia, which I treated by curetting. Some years later the bone began to expand again and, on the second curetting, the tissue removed showed the typical appearances of an osteoclastoma. This second curetting was followed by X-ray treatment and has apparently resulted in a cure.

(3) *Osteoclastomatous cysts.*—As already mentioned, in some bone-cysts there is a certain amount of soft solid tissue around the margin. This tissue contains large numbers of giant cells and, if examined by itself, would be called an osteoclastoma. There is an excellent specimen showing this in the Museum of the Royal College of Surgeons (1637), and I have seen several others. This group is, I think, important, as illustrating the relationship of cysts to osteoclastomata.

The diagnosis of cysts and osteoclastomata.—As long ago as 1912 I endeavoured to emphasize the difficulty in diagnosing conditions which appear cystic in a skiagram and which are actually expanding bone. I do not believe that it is possible to diagnose the nature of such a condition with certainty by any method except exploratory incision and histological examination. By means of the clinical history, site, associated conditions, biochemistry, etc., it may be possible to make a reasonably accurate guess, but that is all. Exploratory operation is essential for accuracy.

(4) *Diffuse fibrosis of bone.*—In certain cases the outstanding feature is the replacement of bone and marrow by a massive formation of fibrous tissue in which small fragments of bone are embedded.

The first case of this kind that I saw was in a boy, aged 10, who was operated upon by Sir Robert Jones in 1906. The tibia was expanded and bent at its centre. A wedge was removed to correct the deformity and was sent to me for investigation. There was no cortex or medulla; the whole wedge consisted of a uniform mass of fibrous tissue containing numerous fragments of bone, which showed active osteoclastic absorption.

There is a beautiful specimen of this condition in the Museum of University College Hospital. The case was recorded in the *Transactions of the Pathological Society* in 1885. This specimen shows very clearly the sharply defined limits of the disease, a point that can usually be made out in good X-ray photographs.

I have operated upon other cases in which this disease was localized to the upper part of the femur. All the cases seem to have occurred in children or adolescents. In one old-standing case, in which the fibrosis was in the shaft of the femur, I found fibro-cartilage in a section.

(5) *Generalized diffuse fibrosis of bone.*—In one class of so-called "generalized osteitis fibrosa," the changes are exactly similar to those just described, but occur in

many bones. The disease begins in childhood or adolescence and has a special predilection for the upper part of the femur and for the tibia. But the changes may be seen in the humerus, fibula, metatarsals, metacarpals, and phalanges, in the pelvis and in the skull. The X-ray photographs show expansion of the bone, disappearance of cortex and medulla, and the sharp margin of the disease, already mentioned. In the skull there are local patches ; the general thickening and alteration of texture seen in cases of hyperparathyroidism do not occur. Sometimes the expanded portion of bone appears so clear that it is thought to be a cyst, but exploration will usually show that the bone contains fibrous tissue. When cysts do occur they are apparently degeneration cysts in the fibrous tissue and not bone-cysts like those previously described.

There are many of these cases now on record. I have myself seen five and have explored the bone in four of these. In two cases the lesions were unilateral.

They can be distinguished from cases of hyperparathyroidism by the clinical history and radiological findings, as well as by the absence of general porosis of the bones, of the characteristic skull changes and of the biochemical changes found in the latter condition.

I think that these two classes—local and generalized diffuse fibrosis of bone—can now be accepted as forming a definite group, recognizable clinically.

(6) *Hyperparathyroidism.*—This condition has been so thoroughly investigated and described that it is only necessary to recapitulate briefly.

The patients may be of either sex and any age, but the condition is more common in women. There is a generalized porosis of bones, with the formation of cysts and osteoclastomata, and thickening and porosity of the skull. There may be great muscular weakness and hypotonicity, and the calcium metabolism shows typical deviation from the normal. The discovery of the cause of this condition and its cure by operation constitute a triumph of biochemical research.

I believe that most of the cases of fibrocystic disease of bone can be included in one of the groups that I have named, and that it is no longer necessary to use the term osteitis fibrosa.

Mr. H. Jackson Burrows dealt from the experimental viewpoint with one of the histological features prominent in (but not peculiar to) fibrocystic bone conditions, namely, the marrow fibrosis. He had observed this change in the course of preliminary experiments, which involved deliberate interference with epiphyseal blood supply.

Lantern slides were shown illustrating the histological changes in the upper capital epiphyses of young rabbits of differing ages, after interference with the blood supply by various procedures ; in each instance the corresponding epiphysis of the control side also was shown. Experimental examples were demonstrated of marrow fibrosis without apparent change in the bone proper, of marrow fibrosis in association with bone necrosis, and of marrow fibrosis in association with both bone necrosis and bone repair ; a condition comparable with the last was seen in a slide illustrating the repair of an area of necrosis in the human subject. A further slide showed that experimental vascular interference sufficient to cause bone necrosis was not in every case followed by marrow fibrosis.

In each quoted instance softening occurred, as indicated by deformity, but decalcification was not demonstrable in X-ray photographs taken by Dr. Simon.

Mr. Jackson Burrows concluded that vascular disturbance in bone might be followed by marrow fibrosis, which was absent from controls, and that this change was independent of lamellar necrosis and of bone repair, though these might accompany it.

Mr. R. Davies-Colley: Much of the confusion and mystery which surrounds this subject is the result of faulty nomenclature.

Although it is universally recognized that the generalized and the focal forms of fibrocystic disease are entirely separate pathological entities, they are grouped together under one name and in the same chapter of the textbook. As long as this is so the confusion will continue.

It would simplify things if the names "osteitis fibrosa" and "fibrocystic disease" were confined to the generalized state which is now recognized to be a metabolic disease, though whether it is always the result of upset in the supply and action of the same hormone is a question which awaits further elucidation.

In these cases the essential feature is osteoporosis and fibrosis of the bones all over the skeleton, and the patchy fibrocystic and osteoclastomatous formations which occur during its course are secondary—and possibly neoplastic—processes resulting from the profoundly altered state of the bones. Osteitis fibrosa seems to me the name best suited to this condition, for it expresses its main features, and it should be included among the metabolic diseases of bone.

In the focal types of fibrocystic disease there is no alteration in the general architecture of the bones, apart from the focal lesion, and there is therefore no reason to suspect a metabolic disorder. If we wish to assign a cause for their occurrence surely the frequency of a history of trauma immediately preceding their development, gives sufficient grounds for believing them to be anomalous reactions or disordered reparative processes in response to injury, and the completeness of their departure from the normal reactions places them among the neoplasias. For what is neoplasia but abnormal and excessive reaction to tissue damage? In this respect fibrocystic disease differs only in degree from the sarcomata. It must be realized that the gap between the sarcomata and the normal reparative processes is bridged by intermediate states which represent every degree of departure from the normal, and it is impossible to define exactly that degree at which it can be said that a state of neoplasia has been reached.

The focal forms of so-called fibrocystic disease, or osteitis fibrosa, seem to fall into two distinct classes—a fibrous group, in which the chief feature is the massive formation of fibrous tissue, often mixed with bone and sometimes showing partial cystic change, and an osteoclastomatous group, in which the appearance ranges from that of a simple cyst to that of a polycystic mass which gradually approaches, in its cellularity and giant-cell formation, the classical osteoclastoma.

The fibrous group comprises a wide range of growths, beginning at one end of the scale with a tumour composed of pure fibrous tissue, generally encapsulated and conforming with the accepted definition of fibroma, and at the other end of the scale reaching a tumour composed of dense bone—the compact osteoma. Between these extremes are intermediate forms illustrating every degree of proportionate admixture of the two substances, bone and fibrous tissue. Encapsulation is confined to the more fibrous forms and, where much bone is present, there is little evidence of it; this probably means that the more bony forms denote a smaller departure from the normal and provoke less reaction around them. Occasionally limitation by a capsule is absent in the fibrous forms and a large part, or the whole shaft, of a long bone may be distended with fibrous growth. It is in this type particularly that degeneration cysts are apt to occur, but they seldom form an important feature of the tumour.

I suggest that the names "osteoma" "osteo-fibroma" "fibroma" and "cystic fibroma" aptly describe these conditions and should be used for them, but it should be clearly understood that they are all essentially of the same nature, varying only in the relative proportion of their main constituents—bone and fibrous tissue.

The osteoclastoma group probably accounts for the vast majority of bone-cysts. Three forms are to be distinguished:—

(*a*) The simple cyst, generally single or numbering two or three at most, with bony wall and surrounded by fibrotic bone but no giant-cell tissue.

(*b*) The polycystic tumour, the cysts separated by bony or fibrous septa containing masses of giant-cell tissue. The tumour is progressive and therefore calls for more radical methods of treatment than the simple cyst.

(*c*) The classical osteoclastoma.

I do not think there need be any hesitation in grouping these three together, because intermediate types occur which prove their close connexion and essential similarity of structure. They should therefore be known as osteoclastomata and cystic osteoclastomata. The cystic varieties are slower growing and less destructive than the classical osteoclastomata, and it is for this reason that they do not invade the epiphyseal line and reach the epiphysis, but tend, as the growth of the bone proceeds, to become separated from it and to approach the middle of the shaft. There is no reason to suppose that the solid forms of osteoclastoma actually arise in the epiphyses. As to why certain forms of osteoclastoma should become cystic, it is possible that the slower-growing forms are more fibrous and less vascular than others, and that they are therefore more liable to œdema and degenerative changes. Hæmorrhage has never seemed to me to be a likely explanation, because even in the more rapidly developing polycystic types, although the contents of the cysts may be slightly blood-stained, there is no staining of their walls or other evidence of profuse hæmorrhage which one would expect if this were their origin.

To sum up: The term "fibrocystic" disease should be restricted to the generalized, or metabolic, disease.

The focal forms are neoplastic in nature and should be included among the tumours of bone. These focal forms fall into two groups, the fibromatous and the osteoclastomatous, and both may develop cysts as the result of degenerative changes.

The vast majority of cysts have an osteoclastomatous origin.

The great difficulty is in fitting in those cases having multiple fibrotic lesions with any particular group; they do not seem to fall in with the metabolic type of disease; Mr. Elmslie has just mentioned several cases of this kind. I prefer to regard these lesions as simply multiple forms of fibroma; they would thus come into line with multiple chondromata which sometimes have a familial tendency. And that brings me to a point which I regard as of great importance, namely, that the hereditary state of bone has an enormous influence on the development of these abnormal reactions. There are two or three examples among the specimens in the Royal College of Surgeons' Museum, of extraordinary skeletons, in which the skull and various long bones show the development of numerous tumours composed of histologically normal bone. In one instance the patient developed sarcoma, and died from it. They are cases of hereditary abnormality of bone, which renders them liable to extravagant overgrowths as a result of outside environment, and probably traumata. I think these multiple fibrous tumours are, most likely, of similar nature and susceptible of a like explanation. I do not think that because they are multiple they should be regarded as related to metabolic disease and to hyperparathyroidism. I would prefer to call them simply "multiple fibromata."

Mr. H. A. T. Fairbank said that he regretted the idea of abandoning the term "osteitis fibrosa," which he had come to regard as appropriate. Admittedly, however, the word "osteitis" was difficult to accept for a condition of bone in which the shaft, or a portion of the shaft, was replaced by a mass of fine-mesh cancellous tissue, with the spaces filled with fibrous tissue. It was a condition in which the

bone formation seemed to be as striking as the fibrous tissue formation, in strong contradistinction to the more general type of fibrocystic disease, in which cavitation of the bone formed a marked feature. Perhaps "hyperostosis fibrosa" would be a suitable term. The condition rarely affected only one bone, but was commonly seen in some bones in the generalized cases.

Mr. Fairbank quoted the following case, which he illustrated by a lantern slide:—

A boy, aged 11, broke his humerus when throwing a cricket ball. There was an area—not sharply marked off—in which the shaft of the bone was apparently replaced by fine cancellous tissue. This bone was explored and the whole of the affected area was found to consist of fine cancellous bone with only one or two minute cavities visible, these and all the smaller spaces being filled with fibrous tissue. It was very much like what was seen in leontiasis of the skull. The bone was simply guttered. The boy was again playing football, but, though the bone was now more solid, he (the speaker) did not think it was entirely cured.

He also reported two cases of multiple fibrocystic disease affecting one side of the body, and not associated with evidence of hyperparathyroidism.

I. A girl, aged 12. X-ray examination of one femur, after a fall, led to the discovery of changes in many bones in the right arm and leg. The bones affected on the right side are: In the arm—the scapula, clavicle (?), humerus, radius, and metacarpals, but not the phalanges. In the leg—the ilium, femur, tibia and fibula, one metatarsal bone and several phalanges. In some of the bones the appearances suggest diffuse osteitic changes rather than cavitation. The only bone on the left side showing any changes is the humerus. The right malar region is rather denser than the left, suggesting the possibility of very early hyperostosis, as was present in the second case.

Blood calcium on three occasions: 11·1; 11·4; 10·2 (i.e. about normal).

Blood phosphorus = 4·76 (slightly too high).

Blood phosphatase = 1·03 (normal with this technique = 0·25).

Complete calcium metabolism investigation showed some increase of excretion of calcium in the urine, and also, but less marked, in the fæces.

Although these findings suggest slight hyperparathyroidism, they are not regarded as sufficiently definite to justify exploration of the neck.

II. A youth, aged 17. First seen when aged 9 years, and then under the care of Mr. Barrington-Ward, on account of leontiasis of the left temporal bone and fibrocystic changes in the long bones of the same side of the body. Microscopic examination of a portion removed from the temporal showed fine cancellous bone with excess of fibroblasts and myeloplaxes in the spaces. Radium was inserted on two occasions.

Skiagrams taken later, including those taken last year, show progressive changes in nearly all the long bones of the left arm and leg. The slow spread of the changes in the bones during the past eight years is obvious.

The deformity of the skull is now marked, and the left eye is proptosed, but vision is unaffected.

In this case the hand is affected as much, or more, than the foot.

Blood phosphorus = 3·18 mgm. per 100 c.c.

Blood calcium = 11·2 mgm. per 100 c.c. (and therefore within normal limits).

Serum phosphatase = 1·1 (normal by this method = 0·25).

It is not considered justifiable to explore the neck in this case.

This case was referred to by Mr. Lawford Knaggs in his book on "Diseases of Bone," with a microscopic section of the affected temporal bone.

Dr. Donald Hunter examined the skiagrams and the biochemical reports of these two cases, and agreed that there was not sufficient evidence of parathyroid hyperplasia to warrant operation on the neck.

Mr. Hermon Taylor: *Chemical aspect and some experimental results.*—The fibrocystic diseases of bone, whether parathyroid or non-parathyroid in type, have,

in common with the other osseous dystrophies, a deficiency of calcium in the skeleton, chiefly as a result of faulty metabolism of this element.

Calcium differs from most other important metabolites in the body, such as sugar or chloride ions, in that there is no conservation of it by the organism. The skeleton, besides being the framework of the body, is the reservoir for calcium, and deprivation of this element results in a constant drain of calcium from the bones into the urine and fæces—a so-called "negative calcium balance." The deprivation may be either an actual insufficiency in the diet, or a deficiency in the amount absorbed from the intestine, or the result of excessive excretion of calcium salts. Calcium can only be absorbed from the intestine in soluble form; precipitation of it in the gut as phosphate or carbonate, or by fatty acids, prevents its absorption. For this reason, excess of phosphate or alkali in the diet, hypochlorhydria, faulty fat absorption due to lack of vitamin D or for other reasons, and possibly errors of protein digestion, may result in osteoporosis.

As in absorption, so in excretion, calcium is influenced by variations in the metabolism of other substances—variations which are reflected in the calcium content of the serum. The serum calcium must be regarded as a solution in biological saturation with the calcium phosphate of the bones, and is normally 9 to 11 mgm. per 100 c.c. This biological saturation is greatly in excess of the ordinary chemical solubility of calcium phosphate, and is dependent on three factors; the concentrations of protein and of phosphate in the serum, and the amount of parathyroid hormone present.

Part of the apparent excess calcium in the serum is due to adsorption of calcium salts on to the serum protein. The amount adsorbed varies directly with the amount of protein present, 1 mgm. of protein being equivalent to 0·5 mgm. of calcium, so that, normally, 2 to 4 mgm. out of the total serum calcium can be ascribed to protein adsorption. The adsorbed calcium salts, however, are not ionized, and are physiologically inactive, but it is necessary to determine the amount of calcium thus put out of action in the serum, before the significance of an abnormal serum calcium can be interpreted.

The remainder of the serum calcium is ionized and is physiologically active. The ions are formed by the dissociation of the calcium phosphate of the bones, but the amount is still in excess of the solubility of calcium phosphate in vitro. This excess of ionized calcium is due to the influence of the parathyroid hormone. The mechanism of this action is not fully understood, but it has been shown, not only that the ionized calcium is reduced after parathyroidectomy and is restored by the administration of parathormone, but that hypercalcæmia can be produced by excess of parathormone and that the degree of hypercalcæmia is proportional to the amount of parathormone given.

Although the dissociation of the calcium phosphate of the bones into calcium and phosphate ions in the serum is promoted in this way by parathormone, the dissociated ions and the solid calcium phosphate are still in equilibrium. They are therefore subject to the Law of Ionic Dissociation, namely, that the concentrations of the calcium and phosphate ions, if altered, must vary inversely with each other to remain in equilibrium with the undissociated salt. Consequently, excess of phosphate ions in the serum from other sources causes a fall in the serum calcium and deposition of calcium phosphate in the bones, while excretion of phosphate as, in acidosis is accompanied by a rise in serum calcium and solution of calcium phosphate from the bones.

Two main factors, therefore, control the balance of calcium between the serum and the bones, the phosphate content and the parathormone content of the serum. Phosphate, however, is intimately concerned with the acid-base metabolism of the body, because the phosphate radical is one of the most important "buffer" ions.

If acidosis is impending, phosphate is excreted to keep the pH of the tissues constant and the serum phosphate falls. Calcium phosphate is dissolved from the bones to restore ionic equilibrium, the serum calcium is raised, and the excess calcium is excreted. Thus acidosis, which occurs in so many conditions, may establish a constant drain of calcium from the bones.

Calcium metabolism then, is dependent upon many outside conditions and circumstances, all of which finally affect the calcium stores of the body, and to them the decalcification of the skeleton observed in many cases of fibrocystic disease can be attributed. All the cases cannot, however, be explained in this way, but the discoveries of phosphatase and parathormone in recent years have helped to elucidate the problem.

With regard to phosphatase, this is an enzyme which hydrolyses organic phosphates into inorganic phosphates, and it occurs at the principal sites of phosphate metabolism—namely, in the intestinal mucosa where phosphorus is absorbed, in the bones where it is stored, and in the kidneys where it is excreted. It is only present in these tissues, however, when and where they are actively functioning. There is practically no phosphatase in the fœtal kidney and the phosphatase of bone occurs only at the sites of active ossification—at the epiphysial line and under the periosteum. It is, in effect, produced by—or concentrated in—the osteoblasts in these situations. It is the local concentration of phosphatase in the osteoblasts that determines ossification; ionized inorganic phosphate is produced in situ from the practically non-ionized organic phosphates of the serum, the local ionic equilibrium is upset, and calcium phosphate is precipitated. This physiological process of calcification to form bone is quite different from the process of pathological calcification such as occurs in tuberculous glands or arterial walls. This type of calcification is always preceded by degeneration of the tissue cells and the fatty acids liberated are precipitated as calcium soaps which gradually change into deposits of calcium carbonate and phosphate.

In view of this important rôle of phosphatase in the process of ossification, the high plasma phosphatase, which occurs in fibrocystic diseases of bone is interesting, and in connexion with this I will mention some experimental work I have done in the last two years. I have been able to show that phosphatase injected into a rabbit over long or short periods of time, in large or small doses, produces no effect whatsoever on the bones. It must be concluded, therefore, that the increased plasma phosphatase is a result of the disease-process in the bones and not the cause of it. Moreover, I have shown that phosphatase in the plasma is very rapidly removed from the circulation, a little by excretion, but mainly by destruction in the body. In generalized disease of bone, therefore, with a continuous high plasma phosphatase, if the enzyme is being continually removed it must also be constantly replaced.

This can be explained on the following hypothesis: Bones undergoing prolonged decalcification, as in fibrocystic disease, are acted upon in two ways. On the one hand is the influence of the decalcifying agent, and on the other the response of the weakened bone, whereby the bone cells are stimulated to form new bone. This they do by an increased output of phosphatase, which, however, is continually swept away into the circulation, causing the high concentration observed in the plasma, where the phosphatase is destroyed. These changes occur independently of the nature of the decalcifying agent, in accordance with the observation that the plasma phosphatase is high in all types of decalcifying disease, whatever the cause.

There still remains the question of the differences between the bones in hyperparathyroidism and those in other types of fibrocystic disease. Ordinary doses of parathormone given to a dog, decalcify the bones through the usual phosphate mechanism. Phosphate is excreted in the urine, the serum phosphate falls, and

therefore the serum calcium rises, as calcium phosphate is dissolved from the bones. The excess of calcium is excreted with the phosphate by the kidney, more calcium phosphate is dissolved from the bones, and so a drain of calcium phosphate from the skeleton into the urine is established. Toxic doses of parathormone, however, result in an increase of phosphate, as well as of calcium, in the serum, so that parathormone may have a direct action on the calcium of the bones, as well as through the medium of phosphate; this action, however, does not appear to come into play with ordinary doses of parathormone.

In the human subject there can be no doubt that the hyperparathyroidism consequent on a parathyroid adenoma does cause Von Recklinghausen's disease, and it has been repeatedly shown that removal of the tumour causes the bones to return gradually to normal. However, not all cases of parathyroid tumour have von Recklinghausen's disease: Forty per cent. of the cases of parathyroid adenomata collected by Barr and Bulger had no bony lesion. Further, many cases of generalized osteitis fibrosa, established by histological examination of a piece of bone removed for section, have shown on biochemical investigation no evidence of hyperparathyroidism: and in not a few such cases a thorough exploration of the neck has failed to demonstrate a tumour, and even normal parathyroids have been removed without effect on the bones. Also we have seen that the decalcifying action of parathormone in ordinary doses is precisely the same as in acidosis, for example, namely, by excretion of phosphate.

Considering all these facts, it is essential not to regard the giant-celled tumours and cysts of von Recklinghausen's disease as necessarily due to hyperparathyroidism. It is of interest to discover, apart from the actual decalcification, the changes that occur in the bones which lead to the fibrosis of the marrow and the formation of the giant-celled tumours and cysts.

In an experiment I performed recently, I was able to produce typical osteitis fibrosa in a rabbit by means of parathormone. The rabbit, however—unlike the dog and, probably, the human being—rapidly develops a compensatory mechanism to the parathormone, so that, whereas in the first stage of injections of parathormone there was a marked loss of calcium in the excreta, the amount of calcium lost rapidly diminished to normal, in spite of continued injections of parathormone. Portions of rib for histological examination were resected in the first stage of decalcification, and in the second stage of recalcification, and show interesting changes. The decalcification of the rib was accompanied in places by hæmorrhages into the marrow, but there was at this stage no fibrosis of the marrow and no giant cells were present. In the stage of recalcification, although the marrow was mostly normal, in places where presumably there had been hæmorrhages, the marrow was replaced by fibrosis and giant cells had appeared = reaction to hæmorrhage. Moreover, the giant cells appeared to be formed by fusion of the proliferating connective tissue cells, and had assumed an osteoclastic function in removing irregular areas of bone.

If these deductions of the histological appearances of the bone at the two stages are correct, it seems that the connective-tissue-cell replacement of the marrow, which occurs in von Recklinghausen's disease, is the reaction to the damage done to the marrow by hæmorrhage during the stage of decalcification; that some of these connective-tissue cells are actively phagocytic in removing the marrow elements; and that the giant cells arise by fusion of phagocytic cells and assume an osteoclastic function in removing irregular islands of bone. This conception agrees with the views of other workers, including Kolodny, who quotes an experiment by Konjetsny, who found that the marrow hæmorrhages produced by direct mechanical trauma were followed either by connective-tissue-cell proliferation, with giant cells of this type, or by the formation of small cysts. Kolodny then supposes that, their phagocytic

function complete, the giant cells remain amongst the connective tissue and form the giant-celled tumours of von Recklinghausen's disease. Bodansky and Jaffe have recently added supporting evidence to this theory, by producing in puppies on a low calcium diet, by means of ammonium chloride, marrow hæmorrhages as well as decalcification. They found that the same fibrosis and giant-cell formation was produced as they themselves had produced by parathormone. The reason for the occurrence of the hæmorrhages therefore appears to be the rapid nature of the decalcification, whereby the local concentration of calcium in the capillary vessels of the bone, damages the endothelium to such an extent that extravasation of blood takes place.

To sum up the position of von Recklinghausen's disease, there are the following points: (1) The hypercalcæmia is definitely due to the hyperparathyroidism and to no other cause. (2) The relatively low phosphorus is an effect of the Law of Ionic Dissociation and is not specific to the parathormone. (3) The high plasma phosphatase is a reaction of the osteoblasts to decalcification, not specific to parathormone. (4) Although the giant-celled tumours and cysts are not necessarily due to hyperparathyroidism, this is, nevertheless, definitely a condition which is likely to cause decalcification of sufficient intensity to produce these effects. (5) Although the excessive excretion of calcium and phosphorus by way of the urine is also not necessarily specific to parathormone, the fact of the loss being confined almost entirely to the urine is a point strongly in favour of hyperparathyroidism.

A typical case of hyperparathyroidism, therefore, presents the radiological appearances of generalized decalcification with cysts, the biochemical characteristics of hypercalcæmia and excessive excretion of calcium in the urine, and the histological picture of marrow fibrosis and giant-celled tumours, but of these only the hypercalcæmia is an absolute indication of hyperparathyroidism.

Dr. John Beattie: In considering disease of bone, one of the most important points is frequently missed, namely, a proper appreciation of the changes which take place in bone during the process of growth. Bone "growth" is not a simple matter of increase in dimensions. "The boy is not the miniature of the man, and the girl is different from the fully-developed woman." In other words, the bony skeleton is dominated by the secretion of one particular gland, namely, the anterior portion of the pituitary gland during the pre-pubertal period. At the time of puberty the gonadal tissue begins to exert its dominant influence, with marked changes in the skeleton.

Now as to more intimate details. If we consider bone growing at the epiphysial line, there are certain factors which are necessary for its formation. First, the cartilage must proliferate, but the cartilage will not proliferate unless there is in the body, apparently, a sufficient quantity of vitamin B. Afterwards the cartilage must be calcified, but calcification will not take place unless there are three factors: (1) vitamin D; (2) plenty of calcium; and (3) sufficient phosphorus. Bone and marrow only differentiate in the presence of vitamin A.

The action of parathormone is not a simple process. If one takes a patient who has suffered from lead-poisoning and injects parathormone into his body, the increased rate of excretion of the calcium due to the rise in the serum calcium is accompanied by increased excretion of lead. In other words, the lead is fixed in the body in the sites where calcium is most mobile. Examined radiologically, it is found that the site of the mobile calcium is the trabeculæ, and apparently parathormone acts on this part of the bony skeleton. It is the diminution in the size of the trabeculæ which is the first radiological change in cases of osteitis fibrosa generalis. The majority of the calcium which is so lost from the bone is excreted in the urine, but there is definite experimental evidence that some of it may be

deposited in other tissues. If parathormone is injected over long periods of time, instead of stimulating the osteoclastic effect, the hormone will eventually cause the formation of osteoblasts. The end-result of that experiment will be an animal with "marble bones." If the doses are sufficiently small and are prolonged for a considerable time there may be no osteoclastic reaction at all, and the whole reaction may be osteoblastic (Selye).

The other influence acting on bone is vitamin D. Excess of this principle gives rise to calcification of areas in the bone which may produce, in the experimental animal, a condition like osteitis deformans, that is to say, the trabeculæ are being gradually appropriated, and the calcium is being taken away and deposited apparently on the cortex. Experimental evidence of transfer of calcium within the bone is well substantiated. When excess of vitamin D is given in large doses, the reverse may take place; there may be absorption of calcium, and the bones may fracture. I need not call your attention to the relation of the lack of vitamin D to rickets and osteomalacia. When the experimental evidence is reviewed, we can only say, with regard to the subject of this discussion, that osteitis fibrosa generalis, or von Recklinghausen's disease, is a disease related to an excess of parathyroid secretion. Physiologically there is no explanation of the disease known as osteitis deformans (Paget's disease), because of all the experimental work which has been done there is only one series of experiments which has produced a condition anything like Paget's disease, and it consisted in giving excess of vitamin D in small doses over a long period of time.

We can throw no light on the other conditions. Osteoclastoma may be due to something in the nature of a localized influence of the parathyroid hormone, though it is almost incredible that it may be so. We want to find out what it is that can cause the localized formation of osteoclasts, and we have no means of doing it experimentally at the moment. I have not been able to find that there are any experiments recorded in the literature bearing on this question. So, from the point of view of the experimentalist, we can only say with regard to "osteitis fibrosa" that it is divisible into: (1) cases of a disease of definitely explained origin, i.e. hyperparathyroidism, and (2) pathological conditions which have not as yet been reproduced experimentally, and which are caused, probably, by many different factors at present unknown.

Dr. G. E. Vilvandré showed lantern slides illustrating a case for which he was indebted to Dr. Donald Hunter. It was a case of osteitis fibrosa, and he (the speaker) was asked to make a radiological examination with a view to discovering a possible parathyroid tumour. He found the tumour in the chest, and he was showing the slides because of the unusual position. A side view of the thorax had aided the diagnosis.

The growth was removed by Mr. A. J. Walton. The sections were made in Professor Turnbull's laboratory and the diagnosis of a parathyroid tumour was confirmed.